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(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.

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#### Description

#### NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

#### BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

#### 35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEQ ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 15 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

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157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

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Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computerreadable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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#### DETAILED DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment 5 that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 10 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag<sup>™</sup> peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide, thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

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"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

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The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

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"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example,  $\alpha$ -globin,  $\beta$ -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

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The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

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A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436. Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, *Nuc. Acids Res.* 14:4683, 1986) are not always exact and may vary by as much as  $\pm$  5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

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### Table 1

<b>D</b>	OFO ID NO	D 11
Protein	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	82	21
AFP310695	. 84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15
111001	90	1.5

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	17
AFP356885	130	17
AFP226938	130	16
AFP138504	134	29
AFP359196	136	
AFP501809	138	24
		27
AFP152733	140	15
AFP541394	142	23
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	. 23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	. 25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270	16
AFP275580	272	28
AFP298054	274	21
AFP348226	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19
	202	

AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	25
	570	

AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	. 19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27

A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein 5 disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the 10 present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

15.

AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and antiviral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., *J. Biol. Chem.* 227:5784-5789, 1996). This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

5 Table 3

	140.00
Locus	Accession Number & Description
AFP130852	AE003823 (fly genomic)
AFP169968	AE003515 (fly genomic)
AFP174843	AF283518 (Mus musculus elongation factor sec)
AFP176427	AE003808 (fly genomic)
AFP178828	PSN_V61483
AFP179530	AE003708 (fly genomic)
AFP188135	AE003677 (fly genomic)
AFP195042	PIR_T41241 (yeast oxysterol-binding protein family)
AFP198645	AE003718 (fly genomic)
AFP199200	AF113691 (human clone FLB4739 PRO1238 mRNA)
AFP204736	AC069237 (human chromosome 3 clone RP11-175M9)
AFP229269	AF247177 (Mus musculus sphingosine-1-phosphate
	phosphohydrolase)
AFP230872	AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AFP279267	AE003559 (fly genomic)
AFP347179	AE003499 (fly genomic) Z1041035F6P
AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP359196	AE003530 (fly genomic)
AFP374312	AE003538 (fly genomic)
AFP389687	AE003831 (fly genomic)
AFP395942	AB041564 (mouse brain cDNA; clone MNCb-0914)
AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP477303	AE003778 (fly genomic)
AFP62060	PSP_Y94938 (Human secreted protein clone ye78_1)
AFP71288	AL161655 (human chromosome 20 clone RP11-116E13)
AFP74517	PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone: RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

Locus	Accession Number & Description
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology
	to PSP_W35393 Human TB2 gene product)
AFP202885	AB037808 (human mRNA for KIAA1387 protein)
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)
AFP250422	AF208849 (human BM-007 mRNA)
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to
	major facilitator protein homolog, fission yeast: PIR_S62432)
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak
	homology to dinitrogenase reductase activating glycohydrolase (draG)
	Archaeoglobus fulgidus: PIR_C69465)
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on
	chromosome 10. Contains a novel gene and the 5' end of the gene for a
	novel protein; ortholog of mouse FISH protein) .
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:
	Human O-linked GlcNAc transferase mRNA)

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker 5 peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically 10 engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to  $E.\ coli\ \beta$ -galactosidase (1,021 residues; see Casadaban et al.,  $J.\ Bacteriol.\ 143:971-980,\ 1980)$ , a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

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Nucleotide Resolutions Complement Resolutions Α Α T T C C G G G G C  $\mathbf{C}$ T T Α Α R Y C|TAG Y C|TA|GR G|TM A|C K K G|TAC M S CIG S CIG W A|TAIT W H A|C|T D A|G|T CIGIT V A|C|G В V AICIG CGT В D AIGIT Η A|C|T N A|C|G|T N A|C|G|T

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter	•	Degenerate
Acid	Code	Codons	Codon
Cys	С	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	A	GCA GCC GCG GCT	GCN
Gly .	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR .
His	Н	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTC TTT	TTY
Туг	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	•	TAA TAG TGA	TRR
Asn Asp	В		RAY
Glu Gln	Z	•	SAR
Any	X		NNN
Gap	-		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

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exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

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### Table 8

AFP152733	K562 cells
AFP169796	T-cells
AFP173341	testis
AFP17588	fetal liver or spleen
AFP194554	fetal liver or spleen
AFP199922	testis
AFP229269	placenta
AFP237679	fetal liver or spleen
AFP257094	adult brain
AFP258118	epidermal breast keratinocytes
AFP263430	breast
AFP276202	infant brain
AFP287436	testis
AFP290397	testis
AFP306591	fetal heart
AFP325761	K562 cells
AFP352125	testis
AFP359138	infant brain
AFP369635	germinal center B-cells
AFP409112	kidney
AFP483037	neonatal keratinocytes
AFP49026	peripheral blood eosinophils of asthma patients
AFP545268	K562 cells
AFP561930	fetal liver or spleen
AFP62060	testis
AFP62197	pregnant uterus
AFP93743	germinal center B-cells
AFP98983	fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex Taq<sup>TM</sup>; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or Advantage<sup>TM</sup> 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

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Table 9, continued	Protein	AFP324816	AFP325761	AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517	AFP93743
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peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H<sub>2</sub>O; 22, genomic DNA. Y=yes; n=no; nd=not determined. Tissues screened were: 1, brain; 2, heart; 3, kidney; 4, liver; 5, lung; 6, pancreas; 7, placenta; 8, skeletal muscle; 9, colon; 10, ovary; 11,

Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

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The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable), digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

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Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning et al., *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (e.g., Sf9 or Sf21 cells) or *Trichoplusia ni* (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10<sup>5</sup> cells to a density of 1-2 x 10<sup>6</sup> cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, *ibid.*; O'Reilly et al., *ibid.*; Richardson, *ibid.*). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

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Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides 5 therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POTI vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. 15 Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (*Bangalore*) 11:47-58, 1987.

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Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

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Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

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Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including 5 exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, J. Am. Chem. Soc. 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, Chem. Pept. Prot. 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the Cytosensor™ Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

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Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., *Investigational New Drugs* 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, *Methods Enzymol.* 109:749-773, 1985; Wahl et al., *Mol. Cell Biol.* 8:5016-5025, 1988; and Cook et al., *Analytical Biochem.* 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., *J. Immunol. Methods* 82:169-179, 1985), and use of tetrazolium salts (Mosmann, *J. Immunol. Methods* 65:55-63, 1983; Alley et al., *Cancer Res.* 48:589-601, 1988; Marshall et al., *Growth Reg.* 5:69-84, 1995; and Scudiero et al., *Cancer Res.* 48:4827-

4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

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In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO<sub>2</sub> atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. <sup>3</sup>H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, J. Immunol. Methods 120:271-276, 1989; Greenfeder et al., J. Biol. Chem. 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as <sup>3</sup>H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, ibid.).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using <sup>3</sup>H-proline incorporation into nascent secreted collagen.

SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1β and TNFα levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

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Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (*J. Biol. Chem.* 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately  $10^4$  -  $10^5$  cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-10 429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. 183:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys, Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 $\alpha$  or IL-1 $\beta$  is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g.,  $\gamma$  counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol*: 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol*. 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACore<sup>TM</sup>, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic 5 peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant  $K_i$  is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin 15 (Steiner et al., <u>J. Biol. Chem.</u> 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. <u>270</u>:25411-25417, 1995).

Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., *J. Biol. Chem.* 263:14621-14624, 1988; Wu et al., *J. Biol. Chem.* 267:963-967, 1992; and Johnston and Tang, *Meth. Cell Biol.* 43:353-365, 1994.

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Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition in vivo. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, Brit. J. Dermatol.

118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive 5 days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB<sub>4</sub> levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton et al. (*ibid.*) and Loddick et al. (*ibid.*).

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The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO<sub>2</sub>/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine* 

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). A test substance is injected subcutaneously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, Advan. Enzyme Regul. 35:293-301, 1995; Conway et al., Clin. Exp. Metastasis 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, Semin. Thromb. Hemost. 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002, 1984.

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Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Ta</u>	<u>ble 10</u>		
<u>Protein</u>		<u>Hexa</u>	peptide N	-termini	
AFP210015	389	405	97	388	359
AFP170681	51	334	113	49	140
AFP413680	221	207	220	206	198
AFP483037	219	218	82	216	215
AFP230872	189	188	73	156	68
AFP178828	211	210	209	208	207
AFP200134	150	149	146	132	145
AFP195796	99	97	111	208	240

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	[284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	. 329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23 .	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885 -	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	. 29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	. 102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	592	591	374	525
AFP75785	128	127	136	<sup>.</sup> 99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64 -	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71 -	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	1.1.8	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922.	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44 ·	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77 ·	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

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AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')2 and Fab fragments, single chain antibodies, and the like, including genetically engineered 5 antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire nonhuman variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K<sub>a</sub>) of 10<sup>6</sup> M<sup>-1</sup> or greater, preferably 10<sup>7</sup> M<sup>-1</sup> or greater, more preferably 10<sup>8</sup> M<sup>-1</sup> or greater, and most preferably 10<sup>9</sup> M<sup>-1</sup> or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, Ann. NY Acad. Sci. 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity *in vitro* and *in vivo*.

The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, Pseudomonas exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary 5 polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., ibid., ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, the **OMIM<sup>TM</sup>** Hopkins Database, Johns University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

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Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

		•	Ta	Table 11			
AFP	GenBank Acc. No.	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
AFP127023	AP001155	RP11-594B10	*	18	18q12	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	11	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	51	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	51		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11-	*	14	14q23.3	62132030	62313415
AFP179530	AC011475	CTC-539A10	*	12	12q12	41234876	41456630
AFP188135	AC013740	#	*	6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	16	16922.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	16	16q11.2	44574019	44904017
AFP:199200	CNS01DV7	BAC-R-1070N10	*	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14q21.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	60169Z	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055 3	3	3q13.12	116466893	116517043
AFP249599	AL157714	RP11-541H12	*	1	1q22-23.3	161893354	162136704
AFP250422	AC012046	RP11-312P12	*	01	10q22.1	81289799	81650062
AFP262739	AC005884	hRPK.264_B_14	*	11	17q23.3	64245127	64365313
AFP275580	AC016773	*	*	3	3q21.3	141329005	141513510
AFP277451	AC055822	RP11-707M3	*	8	8q13.3	75395740	75583383
AFP279267	*	*	AI566086	. 01	10q11.1	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	10	10q24.32	115276306	115467187
AFP290397	*	*	AA421069	15	15q15.3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	*	W52728	11	11911	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP325761	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

20153358	44286594	126134148	138765140	128134589	3500834	4222465	143641730	1514256	59940397	19003942	173547400	70471703	16677574	50564907	60714738	108794286	137478427	*	77633569
19959493	44087441	125918909	138667522	128134250	3479999	4189155	142961410	1512179	59897688	18993217	173540737	70222075	16491516	50554924	60450247	108494503	137477811	*	77419530
14p11.1	17q21.2	12q24.23	1q12-21.2	11q23.3	16p13.3	16p13.3		4p16.3	19q13.33	8p21.3	5q33.1	16q22.1	19p13.13	6p21.1	13q21.1	13q34	6q22.33	1p35.1-36.13	4q21.22
14	17	12	1	=	16	16	7 .	4	19	∞	5	16	19	9	13	13	9	1	4
AI525611	*	*	*	AI253088	AI741157	*	AI133727	AI341602	*	AI814257	A1140615	*	*	AW583171	*	*	AA493506	*	*
BAC-R-407N17	CTD-2534121	*	3.28E+21	*	*	*	*	*	cosmid-R31181	*	*	RP11-502K10	CTB-5E10	*	RP11-342J4	RP11-391H12	*	RP5-1056L3	RP11-791G16
AL132639	AC015936	AC025740	AL022240	*	*	AC004235	*	*	AC006942	*	*	AC009131	AC008686	*	AL138695	AL136221	*	HS1056L3	AC067942
AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517	AFP93743

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet 15 et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other 5 binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a 15 ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

The bioactive conjugates described herein can be delivered intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

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For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

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Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDraw<sup>TM</sup> (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds. x-ray crystallography to determine the three-dimensional structure in atomic detail. nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

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students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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### **EXAMPLES**

## Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His<sub>6</sub> tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique SmaI site just downstream of the MBP-His<sub>6</sub>-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of SmaI-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura<sup>+</sup> transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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## Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (*ibid.*). 100-ml cultures in minimal glucose media containing casamino acids and 100 μg/ml ampicillin are grown at 37°C in 500-ml baffled flasks to  $OD_{600} \approx 0.5$ . Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at 70°C.

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#### Example 3

For larger-scale protein preparation, 500-ml cultures of *E. coli* BL21 expressing the AFP-MBP-His<sub>6</sub> fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH<sub>2</sub>PO<sub>4</sub>, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 μg/ml Leupeptin, 2 μg/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

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# Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with SmaI, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (*S. cerevisiae*) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H<sub>2</sub>O]) and incubated at 30°C. After about 48 hours, the Ura<sup>+</sup> yeast

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transformants from a single plate are resuspended in 1 ml H<sub>2</sub>O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 µl acid-washed glass beads and 200 µl phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 µl ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 µl H<sub>2</sub>O.

Transformation of electrocompetent *E. coli* host cells (Electromax DH10B<sup>TM</sup> cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% Bacto<sup>TM</sup> Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl<sub>2</sub>, 10 mM MgSO<sub>4</sub>, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% Bacto<sup>TM</sup> Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO<sub>2</sub>, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (Lipofectamine<sup>TM</sup> Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

mixed with 605 µl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 µM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## **CLAIMS**

#### We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEO ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- An expression vector comprising the following operably linked 11. elements:
  - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
  - a transcription terminator.
- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- A method of producing a polypeptide comprising culturing the cell of 14. claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
  - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

a transcription promoter;

- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

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#### SEQUENCE LISTING

<110> ZymoGenetics. Inc. <120> NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM <130> 99-20PC <150> US 60/160,712 <151> 1999-10-20 <160> 423 <170> FastSEO for Windows Version 3.0 <210> 1 <211> 1641 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1641) <400> 1 atg tgc tct ctg ggg ttg ttc cct cct cca ccg cct cgg ggt caa gtc 48 Met Cys Ser Leu Gly Leu Phe Pro Pro Pro Pro Pro Arg Gly Gln Val 10 acc cta tat gag cac aat aac gag ctg gtg acg ggc agt agc tat gag 96 Thr Leu Tyr Glu His Asn Asn Glu Leu Val Thr Gly Ser Ser Tyr Glu 20 25 30 ago cog coc coc gao tto ogg ggo cag tgg ato aat ott cot gto ota 144 Ser Pro Pro Pro Asp Phe Arg Gly Gln Trp Ile Asn Leu Pro Val Leu 35 40 45 caa ctg aca aag gat ccc cta aag acc cct gga agg ctg gac cat ggc 192 Gln Leu Thr Lys Asp Pro Leu Lys Thr Pro Gly Arg Leu Asp His Gly 55 aca aga act gcc ttc atc cat cac cgg gag caa gtg tgg aag aga tgc 240 Thr Arg Thr Ala Phe Ile His His Arg Glu Gln Val Trp Lys Arg Cys 70 75 80

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			-	-	gtg Val					-			_		288
					gtg Val				_		_	_		ggc Gly	336
	_	-		-	cga Arg		-							_	384
		-			agg Arg 135	-	-	_	_		_	-		-	432
					agc Ser	-	-	-	-	-		-			480
					gca Ala		-	_		-	-		_	-	528
					acc Thr		-			_	_			_	576
_					ctg Leu	-		-			-	-		•	624
					agc Ser 215										672
					ccc Pro										720
					gtt Val		-	-	_		-		_		768

	cgg Arg							-	-				_		816
	gtc Val				-	-						-			864
	gtg Val 290		_							-			_	~	912
	act Thr			-		_	-	-		-	-	-			960
_	gag Glu							-	-	-			-		1008
_	cca Pro	-	 -	-	_	-			_	_				_	1056
	tac Tyr														1104
	gga Gly 370				_	-			-	-	_				1152
	ata Ile														1200
	atg Met		 -		_		-	_	_	_			_		1248
	aag Lys		 -	_	-				_					_	1296

						ttt Phe										1344
				_	-	ccc Pro 455	-									1392
			-	_		agt Ser							-		•	1440
						gtc Val		-	-			-		_		1488
				-	_	gaa Glu			-							1536
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						cca Pro 535		_	_						tcc Ser.	1632
cac His 545	ctc Leu	taa *				•										1641
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1 Thr	Leu	Tyr	G1u 20	5 His	Asn	Asn	Glu	Leu 25	10 Val	Thr	Gly	Ser	Ser 30	15 Tyr	Glu	

Ser	Pro	Pro 35	Pro	Asp	Phe	Arg	Gly 40	Gln	Trp	Пe	Asn	Leu 45	Pro	Val	Leu
Gln	Leu 50	Thr	Lys	Asp	Pro	Leu 55	Lys	Thr	Pro	Gly	Arg 60	Leu	Asp	His	Gly
Thr 65	Arg	Thr	Ala	Phe	11e 70	His	His	Arg	Glu	G1n 75	Val	Trp	Lys	Arg	Cys 80
He	Asn	Ile	Trp	Arg 85	Asp	Val	Gly	Leu	Phe 90	Gly	Val	Leu	Asn	G1u 95	He
Ala	Asn	Ser	G1u 100	Glu	Glu	Val	Phe	G1u 105	Trp	۷a٦	Lys	Thr	Ala 110	Ser	Gly
Trp	Ala	Leu 115	Ala	Leu	Cys	Arg	Trp 120	Ala	Ser	Ser	Leu	His 125	Gly	Ser	Leu
Phe	Pro 130	His	Leu	Ser	Leu	Arg 135	Ser	Glu	Asp	Leu	Ile 140	Ala	Glu	Phe	Ala
G1n 145	Val	Thr	Asn	Trp	Ser 150	Ser	Cys	Cys	Leu	Arg 155	Val	Phe	Ala	Trp	His 160
Pro	His	Thr	Asn	Lys 165	Phe	Αla	Val	Ala	Leu 170	Leu	Asp	Asp	Ser	Val 175	Arg
			Ala 180		•			185				_	190	_	
		195	Val				200	-				205			
Leu <sub>.</sub>	Ala 210	Val	Ala	Cys	Gln	Ser 215	Cys	He	Leu	He	Trp 220	Thr	Leu	Asp	Pro
Thr 225	Ser	Leu	Ser	Thr	Arg 230	Pro	Ser	Ser	Gly	Cys 235	Ala	Gln	Val	Leu	Ser 240
His	Pro	Gly	His	Thr 245	Pro	Val	Thr	Ser	Leu 250	Ala	Trp	Ala	Pro	Ser 255	Gly
			Leu 260					265	•				270		
		275	Thr				280				-	285		-	•
	290		Asn			295					300				
Thr 305	Thr	Pro	Ser	Ala	Val 310	Phe	Arg	Val	Trp	G1u 315	Ala	Gln	Met	Trp	Thr 320
Cys	Glu	Arg	Trp	Pro 325	Thr	Leu	Ser	Gly	Arg 330	Cys	Gln	Thr	Gly	Cys 335	Trp
Ser	Pro	Asp	G1y 340	Ser	Arg	Leu	Leu	Phe 345	Thr	Val	Leu	Gly	G1u 350	Pro	Leu
Пe	Tyr	Ser 355	Leu	Ser	Phe	Pro	G1u 360	Arg	Cys	Gly	Glu	G1y 365	Lys	Gly	Cys
Val	Gly 370	Gly	Ala	Lys	Ser	A1a 375	Thr	Пe	Val	Ala	Asp 380	Leu	Ser	Glu	Thr

6

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Thr 385	Ile	Gln	Thr	Pro	Asp 390	Gly	Glu	Glu	Arg	Leu 395	Gly	Gly	Glu	Ala	His 400		
Ser	Met	Val	Trp	Asp 405	Pro	Ser	Gly	Glu	Arg 410	Leu	Ą٦a	Val	Leu	Met 415	Lys		
Gly	Lys	Pro	Arg 420	Val	Gln	Asp	Gly	Lys 425	Pro	Val	Ile	Leu	Leu 430	Phe	Arg		
Thr	Arg	Asn 435	Ser	Pro	Val	Phe	G1u 440	Leu	Leu	Pro	Cys	Gly 445	Ile	Ile	Gln		
Gly	G1u 450	Pro	Gly	Ala	Gln	Pro 455	Gln	Leu	Пe	Thr	Phe 460	His	Pro	Ser	Phe		
465	Lys				470				·	475					480	÷	
	Ile			485					490					495			
	Leu		500					505					510				
	Asp	515					520					525			•		
	Pro 530	Leu	Pro	Gly	Pro	Pro 535	Pro	VаI	Leu	Pro	H1S 540	Ser	Pro	His	Ser		
545	Leu														٠		
		210>	3 1233														
	<2	212>	DNA		oiens												
		220>	TIOM	յ Տար	o i en s												
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					ature												
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-4-		<b>100&gt;</b>	_	-4-										4.4.			40
	gag Glu							-									48
	gcc																96
Pro	Ala	Ser	Glu 20	He	Ala	Lys	Leu	Leu	Ala	Ser	Asp	Asp	Met	Asn	Пе		

		_				_		-	ctt Leu				•	•		144
_	_	-	-	-			-		agt Ser			_	-			192
					-		_		ctg Leu		-	-	-			240
					-		_	_	cag Gln 90				-	_	-	288
-	_							-	cga Arg		_			_		336
					_			_	ggt Gly				_	-		384
							_		agc Ser		_	_		_		432
							-	-	aat Asn	_						480
							-	-	aaa Lys 170	_			-			528
									gta Val		-					576
				_		_			atg Met				_			624

	ggt Gly 210			_	-					-	_				672
	ggc Gly			_				-	-		-		_	-	720
-	cag Gln			-	•		_					•		_	768
	gtg Val								_				_	-	816
	agt Ser					-	_	-		-					864
	tgg Trp 290				_	_							-		912
	acg Thr				_	_		-					-	_	960
	gca Ala		_			_			-	-		-	_		1008
	ccc Pro														1056
_	gat Asp	-	 	-	-				-	-			_	-	1104
	999 Gly 370													_	1152

9

ccc cag aca aat gag tgg acc cag gtt gct cca ctg tgc cta gga aga 1200 Pro Gln Thr Asn Glu Trp Thr Gln Val Ala Pro Leu Cys Leu Gly Arg 385 390 395 gct gga gct tgt gtt gtg act gta aaa tta taa 1233 Ala Gly Ala Cys Val Val Thr Val Lys Leu \* 405 410 <210> 4 <211> 410 <212> PRT <213> Homo sapiens <220> <221> VARIANT. <222> (1)...(410) <223> Xaa = Any Amino Acid <400> 4 Met Glu His Phe Met Glu Val Ile Arg Asn Gln Glu Phe Val Leu Leu 10 Pro Ala Ser Glu Ile Ala Lys Leu Leu Ala Ser Asp Asp Met Asn Ile 25 Pro Asn Glu Glu Thr Ile Leu Asn Ala Leu Leu Thr Trp Val Arg His Asp Leu Glu Gln Arg Arg Lys Asp Leu Ser Lys Leu Leu Ala Tyr Ile 55 Arg Leu Pro Leu Leu Ala Pro Gln Phe Leu Ala Asp Met Glu Asn Asn Val Leu Phe Arg Asp Asp Ile Glu Cys Gln Lys Leu Ile Met Glu Ala 85 90 Met Lys Tyr His Leu Leu Pro Glu Arg Arg Pro Met Leu Gln Ser Pro 105 100 110 Arg Thr Lys Pro Arg Lys Ser Thr Val Gly Thr Leu Phe Ala Val Gly 120 125 Gly Met Asp Ser Thr Lys Gly Ala Thr Ser Ile Glu Lys Tyr Asp Leu 140 135 Arg Thr Asn Met Trp Thr Pro Val Ala Asn Met Asn Gly Arg Xaa Leu 145 150 155 160 Gin Phe Gly Val Ala Val Leu Asp Asp Lys Leu Tyr Val Val Gly Gly 165 170 Arg Asp Gly Leu Lys Thr Leu Asn Thr Val Glu Cys Tyr Asn Pro Lys

180 185 190 Thr Lys Thr Trp Ser Val Met Pro Pro Met Ser Thr His Arg His Gly 200 Leu Gly Val Ala Val Leu Glu Gly Pro Met Tyr Ala Val Gly Gly His 220 Asp Gly Trp Ser Tyr Leu Asn Thr Val Glu Arg Trp Asp Pro Gln Ala 230 235 Arg Gln Trp Asn Phe Val Ala Thr Met Ser Thr Pro Arg Ser Thr Val 250 Gly Val Ala Val Leu Ser Gly Lys Leu Tyr Ala Val Gly Gly Arg Asp 265 260 Gly Ser Ser Cys Leu Lys Ser Val Glu Cys Phe Asp Pro His Thr Asn 280 Lys Trp Thr Leu Cys Ala Gln Met Ser Lys Arg Arg Gly Gly Val Gly 295 300 Val Thr Thr Trp Asn Gly Leu Leu Tyr Ala Ile Gly Gly His Asp Ala 310 315 Pro Ala Ser Asn Leu Thr Ser Arg Leu Ser Asp Cys Val Glu Arg Tyr 325 330 Asp Pro Lys Thr Asp Met Trp Thr Ala Val Ala Ser Met Ser Ile Ser 345 Arg Asp Ala Val Gly Val Cys Leu Leu Gly Asp Lys Leu Tyr Ala Val 360 Gly Gly Tyr Asp Gly Gln Ala Tyr Leu Asn Thr Val Glu Ala Tyr Asp 375 380 Pro Gln Thr Asn Glu Trp Thr Gln Val Ala Pro Leu Cys Leu Gly Arg 390 400 Ala Gly Ala Cys Val Val Thr Val Lys Leu 405 <210> 5 <211> 1644 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1644) <400> 5 atg ctg cgg tac ctg gag acg gca gac tac gcc atc cgc gag gag atc 48 Met Leu Arg Tyr Leu Glu Thr Ala Asp Tyr Ala Ile Arg Glu Glu Ile 1 10

11 -

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			_							_				gac Asp		144
	_						_			_		_		aac Asn	_	192
														ctc Leu		240
-		-	-				-	7 -	_	-				atc Ile 95		288
	-				_		•		-		_		-	ccc Pro		336
				-				-			-	-	_	gtg Val	-	384
_			•	-	_					•				ctc Leu		432
														tcc Ser		480
														tac Tyr 175		528
														ctg Leu		576

						gag Glu										624
	_	_	_			999 Gly 215	-			-	_	-	_			672
						gac Asp										720
_			-	-		tcg Ser			-	-		-		_		768
						gca Ala			Ala							816
	-			-		gat Asp		-	-	-	-		-	_		864
					-	ttc Phe 295		-					-			912
						gat Asp	-	_	_		_		-	_	-	960
						gag Glu										1008
						ctg Leu										1056
						cag G1n									-	1104

												gtg Val			1152
					-		_					atc Ile		-	1200
_			_	_		-	-	_			-	ttc Phe			1248
				-			_					acc Thr 430			1296
												ttc Phe		-	1344
												atc Ile			1392
			_	_	_	_	-		-	_		ctt Leu	-		1440
												gag Glu			1488
		7			-			_	_	_		ggc Gly 510	_	_	1536
					_	_	_	_	_			ctg Leu		-	1584
							_					ctg Leu		-	1632

14

1644

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			260					265					270		
Leu	Leu	Val 275	Asp	Val	Phe	Asp	Gly 280	Pro	Ala	Ala	Gln	Pro 285	Ser	Leu	Gly
Pro	Thr 290	Pro	Glu	Glu	Ala	Phe 295	Leu	Ser	Pro	Gly	Pro 300	Glu	Asp	Ile	Gly
Pro 305	Pro	Ile	Pro		Ala 310	Asp	Glu	Leu	Leu	Asn 315	Lys	Phe	Val	Cys	Lys 320
Asn	Asn	Gly	Val	Leu 325	Phe	Glu	Asn	Gln	Leu 330	Leu	Gln	Пe	Gly	Val 335	Lys
Ser	Glu	Phe	Arg 340	Gln	Asn	Leu	Gly	Arg 345	Met	Tyr	Leu	Phe	Tyr 350	Gly	Asn
Lys	Thr	Ser 355	Val	Gln	Phe	Gln	Asn 360	Phe	Ser	Pro	Thr	Val 365	Val	His	Pro
Gly	Asp 370	Leu	Gln	Thr	Gln	Leu 375	Ala	Val	Gln	Thr	Lys 380	Arg	Val	Ala	Ala
G1n 385	Val	Asp	Gly	Gly	A1a 390	Gln	Val	Gln	Gln	Va1 395	Leu	Asn	Пe	Glu	Cys 400
Leu	Arg	Asp	Phe	Leu 405	Thr	Pro	Pro	Leu	Leu 410	Ser	Val	Arg	Phe	Arg 415	Tyr
Gly	Gly	Ala	Pro 420	Gln	Ala	Leu	Thr	Leu 425	Lys	Leu	Pro	Val	Thr 430	Įlе	Asn
Lys	Phe	Phe 435	Gln	Pro	Thr	Glu	Met 440	Ala	Ala	Gln	Asp	Phe 445	Phe	Gln	Arg
Trp	Lys 450	Gln	Leu	Ser	Leu	Pro 455	Gln	Gln	Glu	Ala	G1n 460	Lys	Ile	Phe	Lys
A1a 465	Asn	His	Pro	Met	Asp 470	Ala	Glu	Val	Thr	Lys 475	Ala	Lys	Leu	Leu	G1y 480
Phe	Gly	Ser	Ala	Leu 485	Leu	Asp	Asn	Val	Asp 490	Pro	Asn	Pro	Glu	Asn 495	Phe
Val	Gly	Ala	Gly 500	Ile	Ile	G1n	Thr	Lys 505	Ala	Leu	Gln	Val	Gly 510	Cys	Leu
Leu	Arg	Leu 515	Glu	Pro	Asn	Ala	G1n 520	Ala	Gln	Met	Tyr	Arg 525	Leu	Thr	Leu
Arg	Thr 530	Ser	Lys	Glu	Pro	Va1 535	Ser	Arg	His	Leu	Cys 540	Glu	Leu	Leu	Ala
G1n 545	Gln	Phe													

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<211> 711

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<213> Homo sapiens

<220>

16

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Ser Ile Met Ile Gly Val Lys Pro Cys Ile Asp Lys Ser Val Met Glu

155

150

_	•	_	_	-	_	tta Leu					_			528
						aca Thr								576
			-	-		ctt Leu	-		-		-		_	624
_		-	-			gac Asp 215	_					-	-	672
	_				-	gag Glu		-						711

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<211> 236

<212> PRT

<213> Homo sapiens

<400> 8

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	130					135					140					
Ser 145	Ile	Met	Пe	Gly	Val 150	Lys	Pro	Cys	Ile	Asp 155	Lys	Ser	Val	Met	Glu 160	
Ser	Ser	Asp	Arg	Cys 165	Ala	Leu	Ser	Ser	Pro 170	Ser	Leu	Ala	Phe	Thr 175	Pro	
Pro	Пe	Lys	Thr 180	Leu	Gly	Thr	Pro	Thr 185	Gln	Pro	Gly	Ser	Thr 190	Pro	Arg	
Ile	Ser	Thr 195	Met	Arg	Pro	Leu	Ala 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	He	Ser	Asp 215	Arg	Gl'n	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	•
Leu 225	Val	Ser	Lys	Ala	Met 230	Glu	Tyr	Met	Phe	Gly 235	Trp					
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_	cag Gln			_				-			_		-	_	_	48
	gtg Val															96
_	cag Gln		_					_	-	_			_		_	144
	cgc Arg 50			-		-	_									192
	gta Val	•		_	-	_		_			-				_	240

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19

					cat His		-				-	=		_		288
					tcg Ser											336
		-		-	act Thr		-				-		-	-	_	384
_	-				aac Asn							_			-	432
				_	agg Arg 150		_				_	-		_		480
	-			-	tta Leu		-	-						-		528
					tgt Cys											576
_	-		_	-	tat Tyr		_		-							624
	aag Lys 210															636
	<2 <2	?10> ?11> ?12> ?13>	211 PRT	sap	oiens	<b>S</b>										
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Met Gln Leu Ser Leu Thr Gln Ala Arg Thr Trp Lys Gly Leu Leu Leu

Leu	Val	Ser	Cys 20	Met	Ile	Leu	Trp	Ile 25	Ser	Val	Thr	Pro	Thr 30	Pro	Tyr	
Asp	Gln	Met 35	Ser	Asn	Glu	Glu	Leu 40	Tyr	Asp	Asn	Ļeu	Leu 45	Ser	Cys	Ser	
His	Arg 50	Thr	His	Val	Val	Ala 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	Asp	Leu	
Asn 65	Val	Ala	Glu	Arg	Arg 70	Cys	Phe	Lys	Asn	Lys 75	Arg	Asn	Asn	Thr	Cys 80	
His	Thr	Thr	Ser	Thr 85	His	Thr	Ala	Lys	Thr 90	Asn	Glu	Asp	Leu	Leu 95	Lys	
Val	Ile	Ile	Ser 100	Val	Ser	Asn	Ala	Trp 105	Ile	Tyr	Pro	Leu	Lys 110	Met	Leu	
	Pro	115					120					125				
	Ala 130					135	_			Ť	140			·		
145	Phe				150					155					160	
	Val			165					170					175		
	Leu		180			-		185	-				190			
	Lys	195	Lys	Asp	Tyr	Leu	G1n 200	He	Leu	Arg	Pro	Asn 205	He	He	Lys	
Asn	Lys 210	Inp														
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		220>	Homo	. sat	rens	•										
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a <b>t</b> a		<00>		000	++^	202					~~~	~~~	~~~	oot		40
	tcc Ser															48
	ccg Pro					_										96

	20					25					30				
				aac Asn									-		144
				ggc Gly 55						-	-		_		192
				gcg Ala	_			•		-	_	_			240
				ccg Pro		_	-	_	_	_		-			288
				gtg Val			_	_		_	_		_		336
				ccc Pro				-	-			-	_		384
			_	tgc Cys 135			_		-	-	_		-		432
		_	_	cct Pro		-		-				-		`	480
				atc Ile								_			528
				aaa Lys											576
				gaa Glu											624

22

195 200 205

aaa gtg aaa aag gag aga gac cct tga Lys Val Lys Lys Glu Arg Asp Pro \* 210 215 651

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<213> Homo sapiens

<400> 12

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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro 65 70 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro 100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val

165 170 175 Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro

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24

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Leu Thr Lys Phe Asn Lys Glu Asn Asn Cys Val Leu Pro His Ser Lys
Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
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Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro-
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Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr
                                105
Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
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Val Phe Leu Glu Leu Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu
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1				5					10					15			
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_	-					-	-					ttt Phe 45	-			e .	144
				_		_	-					tgg Trp					192
		-	_	-		-					-	ctg Leu					240
					-							cac His		_	-		288
				-			-				-	cag Gln	-	_	-		336
					_	_		-		-		ggc Gly 125	-				384
												cag Gln					432
				-			-	-	_	-		acc Thr	_				480
												cgc Arg					528
												gga Gly					576

26

•

180 185 190 624 gcc ctg agt cta agg tcc agc aca aac ccg gca gat tcc cgg aca gag Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 195 200 gct tct gag gat gac atg gga gac aaa gct ccc aag agg gcc aaa ccc 672 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 210 215 220 atc aaa aaa gcg ccc aaa gct gag cca ctg gct tcc aag aca ctg aag 720 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 225 230 235 240 acc cgg ccc aag aag acc tct ggc ggg ggc gac tca gct tga 765 Thr Arg Pro Lys Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala \* 245 250 <210> 16 <211> 254 <212> PRT <213> Homo sapiens <400> 16 Met Val Ser Trp Ile Ile Ser Arg Leu Val Val Leu Ile Phe Gly Thr 5 Leu Tyr Pro Ala Tyr Ser Ser Tyr Lys Ala Val Lys Thr Lys Asn Val 25 Lys Glu Tyr Val Lys Trp Met Met Tyr Trp Ile Val Phe Ala Phe Phe Thr Thr Ala Glu Thr Leu Thr Asp Ile Val Leu Ser Trp Phe Pro Phe 55 60 Tyr Phe Glu Leu Lys Ile Ala Phe Val Ile Trp Leu Leu Ser Pro Tyr 65 70 75 80 Thr Lys Gly Ser Ser Val Leu Tyr Arg Lys Phe Val His Pro Thr Leu 90 Ser Asn Lys Glu Lys Glu Ile Asp Glu Tyr Ile Thr Gln Ala Arg Asp 105 110 Lys Ser Tyr Glu Thr Met Met Arg Val Gly Lys Arg Gly Leu Asn Leu 115 120 125

Ala Ala Asn Ala Ala Val Thr Ala Ala Ala Lys Gly Gln Gly Val Leu

Ser Glu Lys Leu Arg Ser Phe Ser Met Gln Asp Leu Thr Leu Ile Arg

140

				150					155					160	
G1u	Asp	Ala	Leu 165	Pro	Leu	Gln	Arg	Pro 170	Asp	Gly	Arg	Leu	Arg 175	Pro	
Pro	Gly	Ser 180	Leu	Leu	Asp	Thr	Ile 185	Glu	Asp	Leu	Gly	Asp 190	Asp	Pro	
Leu	Ser 195	Leu	Arg	Ser	Ser	Thr 200	Asn	Pro	Ala	Asp	Ser 205	Arg	Thr	Glu	
Ser 210	Glu	Asp	Asp	Met	Gly 215	Asp	Lys	Ala	Pro	Lys 220	Arg	Ala	Lys	Pro	
Lys	Lys	Ala	Pro	Lys 230	Ala	Glu	Pro	Leu	A1a 235	Ser	Lys	Thr	Leu	Lys 240	
Arg	Pro	Lys	Lys 245	Lys	Thr	Ser	Gly	G1y 250	Gly	Asp	Ser	Ala			
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		CDC													
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			5					10				·	15		ı
															96
Ala	MSII	20	ASP	3111	Ala	ASII	25	Vai	uly	(11)	ıyı	30	Leu	Ald	
											_	_		_	144
Vai	35	Lys	піз	піЗ	GIY	40	Pro	Prie	Tyr	Val	45	Ald	Pro	ser.	
		-		-	_									-	. 192
5er	Lys	ASP	Leu	arg	Leu 55	ыu	ınr	ыу	Ly5	60	116	пе	116	GIU	
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-	cct Pro				_						-	_					288
_	ctc Leu									_		_		-			336
	gag Glu				-												384
	cta Leu 130	-			_	_											408
÷	/	210> 211> 212> 213>	135 PRT	o sar	oiens	5											
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Mot		100>		C1.	V-1	۳۵2	۸٦ -	Val	V-1	บรา	Clv	۸٦ -	۸۵۵	۸۵۵	V-7	٠	
1	Ala			5					10		•			15			
Val	Ala	Asn	Xaa 20	Asp	Thr	Ala	Asn	Lys 25	Val	Gly	Thr	Tyr	GIn 30	Leu	Ala		
Ile	Val	Ala 35	Lys	His	His	Gly	Ile 40	Pro	Phe	Tyr	Val	Ala 45	Ala	Pro	Ser	•	
Ser	Ser 50	Cys	Asp	Leu	Arg	Leu 55	Glu	Thr	Gly	Lys	Glu 60	Пe	Пe	Пе	Glu		
G1u 65	Aṛg	Pro	Gly	Gln	G1u 70		Thr	Asp	Val	Asn 75		Val	Arg	Ile	Ala 80		
	Pro	Gly	Ile	G1 <i>y</i> 85	۷a۱	Trp	Asn	Pro	Ala 90	Phe	Asp	Val	Thr	Pro 95			

29

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			agt Ser								_		•	_		384
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	-	_	ctg Leu	-					_	_	_	_	_	_	_	480
			ggc Gly		-	_						-				528
-		-	gag Glu 180		_			_			_		_		_	576
			cag G1n				_	_				-				624
			ctg Leu		_		-								-	672
			cat His		_	_			_		_		_			720
gct Ala	ttc Phe	att Ile	acc Thr	tgg Trp 245	ttg Leu	gtt Val	aaa Lys	tct Ser	aga Arg 250	ctt Leu	aag Lys	agg Arg	ctc Leu	tgc Cys 255	tcc Ser	768
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	_		_		gaa Glu 150		_									480
	_		_		caa G1n	-									-	528
	_			-	gaa G1u	_	•		_				-		_	·576
					ttc. Phe											624
-					cca Pro				_				-	_	-	672
		-	_		gag G1u 230	-		-			_					720
					ggt Gly											768
					atc Ile	_	-		_							816
					cag Gln											864
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc	912

Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu	
				-										tgt Cys		960
														cac His 335	-	1008
														ggc Gly		1056
														cac His		1104
														agc Ser		1152
														agg Arg		1200
														gcc Ala 415		1248
				_	_		-			_			-	tgc Cys		1296
							_	-	-		_	-		cac His	_	1344
														ggc Gly		1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

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	tcc Ser			_	_			-								1536
	aag Lys	-	-		-		_	-			-			-		1584
	cgc Arg 530						-	-				tga *				1623
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Ser				5					10					15		
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Ser	Ser Glu	Asn	20	Met			Ile	25	Gly			Gly	30	Asn		
	Glu Glu	Asn 35	20 Glu	Met Glu	Glu	Glu Pro	Ile 40	25 Ser	Gly Gln	Gln	Glu Pro	G1y 45	30 Ser	Asn Gly	Asp	
Tyr Phe	Glu	Asn 35 Val	20 Glu Glu	Met Glu Glu	Glu Ile Pro	Glu Pro 55	Ile 40 Phe	25 Ser Gly	Gly Gln Leu	Gln Glu Gln	Glu Pro 60	Gly 45 Gln	30 Ser Ser	Asn Gly Pro	Asp Gly Glu	
Tyr Phe 65	Glu Glu 50	Asn 35 Val Pro	20 Glu Glu Gln	Met Glu Glu Ser	Glu Ile Pro 70	Glu Pro 55 Glu	Ile 40 Phe Phe	25 Ser Gly Glu	Gly Gln Leu Pro	Gln Glu Gln 75	Glu Pro 60 Ser	Gly 45 Gln Pro	30 Ser Ser Arg	Asn Gly Pro Phe	Asp Gly Glu 80	

			100					105					110		
Glu	Phe	G1u 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr
Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
G1u 145	Ser	Ser	Arg	Tyr	Glu 150	Ser	Gln	Asn	Thr	G1u 155	Leu	Lys	Thr	Gln	Ser 160
Pro	Glu	Phe	Glu	Ala 165	Gln	Ser	Ser	Lys	Phe 170	Gln	Glu	Gly	Ala	Glu 175	Met
Leu	Leu	Asn	Pro 180	Xaa	Glu	Lys	Ser	Pro 185	Leu	Asn	IJе	Ser	Val 190	Gly	Val
His	Pro	Leu 195	Asp	Ser	Phe	Thr	G1n 200	Gly	Phe	Gly	Glu	G1n 205	Pro	Thr	Gly
Asp	Leu 210	Pro	Ile	Gly	Pro	Pro 215	Phe	Glu	Met	Pro	Thr 220	Gly	Ala	Leu	Leu
225					230					235		-		Thr	240
				245	-	_			250				_	Gly 255	
			260			-	_	265		-			270	Gly	
		275					280					285		Lys	
	290	_			Ť	295	_		ı		300			Asp	
305				_	310			-		315			-	Cys	320
				325					330					His 335	
			340					345					350	Gly	_
		355	·			-	360					365		His	
	370					375					380			Ser	
385					390					395				Arg	400
Phe	Ser	Cys	Gly	11e 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
He	Pro	His	Ala 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	G1 <i>y</i> 435	Lys	Arg	Phe	Gly	G1n 440	Ser	Ser	Val	Leu	Ala 445	Ile	His	Ala
Δra	Thr	Hic	Leu	Pro	Glv	Ara	Thr	Tyr	Sar	Cvs	Pro	Asn	Cvc	Glv	Lvc

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	450					455					460					
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Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg	
Ser	Ser	Thr	Leu 500	Leu	Gln	His	His	Arg 505	Val	His	Ser	Gly	Glu 510	Arg	Pro	
Tyr	Lys	Cys 515	Asp	Asp	Cys	Gly	Lys 520	Ala	Phe	Ser	Gln	Ser 525	Ser	Asp	Leu	
Ile	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg	Arg 540		-			
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					ggc Gly											192
					cct Pro ·70											240
			-		gtg Val											288

38

85 90 95 aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cqc 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly \* 130 135 140 <210> 24 <211> 143 <212> PRT <213> Homo sapiens <400> 24 . Met Glu Pro Ala Leu Arg Ala Val Cys Lys Asp Val Arg Ile Gly Thr 10 Ile Leu Ile Gln Thr Asn Gln Leu Thr Gly Glu Pro Glu Leu His Tyr Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp 40 45 Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu 55 Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 85 90 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 120 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly 130 135 140

<210> 25

<211> 912

<212> DNA

<213> Homo sapiens

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39

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Gly Arg Arg Asn Tyr Arg Phe Phe Tyr Ala Phe Ile Leu Ser Leu Ser

40

145					150					155					160	
														acg Thr 175		528
	_	_		_						_	_			cca Pro	_	576
-		_		_			_							att Ile	_	624
														act Thr		672
														gag Glu		720
														tgt Cys 255		768
		_						-			-			gga Gly		816
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-	tgc Cys 290	_	_	-		-	-	-	_	-				ccć Pro	tga *	912

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<211> 303

<212> PRT

<213> Homo sapiens

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<211> 795

<212> DNA

<213> Homo sapiens

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	130					135					140						
-			-			_		_	-	_			_	aat Asn			480
	_		-					-		-	-	-	-	aag Lys 175	-		528
														ttc Phe			576
		_	_	-	-					_			_	gtg Val	_		624
														aca Thr			672
						_		_		_	_	-		tta Leu			720
				_	-		-	-	-	-	-	-	-	tcc Ser 255			768
					ctt Leu			taa *									795
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<211> 711

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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WO 01/29221

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			_	_	tac Tyr	_										96
					ctc Leu											144
		-			tat Tyr	_	-	_			_	-			_	192
				-	ctg Leu 70										-	240
_	-	-			ttg Leu				-				-			288
-			-	-	ttg Leu						-	-				336
				_	agt Ser			-		-			-			384
					gtt Val	-										432
-		_	-		gat Asp 150	-								-		480
cag	ctg	gct	gga	ctg	aca	ttg	ttg	aca	aac	atg	act	gtt	acc	aat	gac	528

PCT/US00/29052

									46							
G1n	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp	
	-		_		cac His	_				_	_		•			576
					aac Asn										_	624
					cca Pro		-						-	-		672
_	_				ctt Leu 230			-		•	_	tag *				711
		210> 211> 212> 213>	236 PRT	o sap	oiens	5	•									
	</th <th>100&gt;</th> <th>30</th> <th></th>	100>	30													
Met 1	Gly	Gly	Pro	Arg	Gly	Ala	Glv	T								
GIV				5			uij	irp	Val 10	Ala	Ala	Gly	Leu	Leu 15	Leu	
uij	Ala	Gly	A1a 20		Tyr				10					15		
_			20	Cys	Tyr Leu	Cys	Ile	Tyr 25	10 Arg	Leu	Thr	Arg	Gly 30	15 Arg	Arg	
Arg	Gly	Asp 35	20 Arg	Cys Glu	•	Cys Gly	Ile Ile 40	Tyr 25 Arg	10 Arg Ser	Leu Ser	Thr Lys	Arg Ser 45	Gly 30 Ala	15 Arg Glu	Arg Asp	
Arg Leu	Gly Thr 50	Asp 35 Asp	20 Arg Gly	Cys Glu Ser	Leu	Cys Gly Asp 55	Ile Ile 40 Asp	Tyr 25 Arg Val	10 Arg Ser Leu	Leu Ser Asn	Thr Lys Ala 60	Arg Ser 45 Glu	Gly 30 Ala Gln	15 Arg Glu Leu	Arg Asp Gln	
Arg Leu Lys 65	Gly Thr 50 Leu	Asp 35 Asp Leu	20 Arg Gly Tyr	Cys Glu Ser Leu	Leu Tyr Leu	Cys Gly Asp 55 Glu	Ile Ile 40 Asp Ser	Tyr 25 Arg Val	10 Arg Ser Leu Glu	Leu Ser Asn Asp 75	Thr Lys Ala 60 Pro	Arg Ser 45 Glu Val	Gly 30 Ala Gln Ile	15 Arg Glu Leu Ile	Arg Asp Gln Glu 80	
Arg Leu Lys 65 Arg	Gly Thr 50 Leu Ala	Asp 35 Asp Leu Leu	20 Arg Gly Tyr Ile	Cys Glu Ser Leu Thr 85	Leu Tyr Leu 70	Cys Gly Asp 55 Glu Gly	Ile Ile 40 Asp Ser Asn	Tyr 25 Arg Val Thr	10 Arg Ser Leu Glu Ala 90	Leu Ser Asn Asp 75 Ala	Thr Lys Ala 60 Pro	Arg Ser 45 Glu Val	Gly 30 Ala Gln Ile Val	15 Arg Glu Leu Ile Asn 95	Arg Asp Gln Glu 80 Gln	

Asn Leu Ser Val Asn Val Glu Asn Gln Ile Lys Ile Lys Ile Tyr Ile

Ser Gln Val Cys Glu Asp Val Phe Ser Gly Pro Leu Asn Ser Ala Val 145 150 155 160 Gln Leu Ala Gly Leu Thr Leu Leu Thr Asn Met Thr Val Thr Asn Asp 170 165 175 His Gln His Met Leu His Ser Tyr Ile Thr Asp Leu Phe Gln Val Leu 185 Leu Thr Gly Asn Gly Asn Thr Lys Val Gln Val Leu Lys Leu Leu Leu 200 Asn Leu Ser Glu Asn Pro Ala Met Thr Glu Gly Leu Leu Arg Ala Gln 210 215 220 Val Asp Ser Ser Phe Leu Ser Leu Met Thr Ala Thr 225 230 <210> 31 <211> 1737 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1737) <400> 31 atg cgc gct gcc cgc gcc gcg ccg ctg ctc cag ctg ctc ctg ctg 48 Met Arg Ala Ala Arg Ala Ala Pro Leu Leu Gln Leu Leu Leu Leu 1 15 ggg ccg tgg ctg gag gct gcg ggc gtt gcg gag tcg ccg ctg ccc gcc 96 Gly Pro Trp Leu Glu Ala Ala Gly Val Ala Glu Ser Pro Leu Pro Ala 20 25 gtg gtc ctt gcc atc ctg gcc cgc aat gcc gaa cac tcg ctg ccc cac 144 Val Val Leu Ala Ile Leu Ala Arg Asn Ala Glu His Ser Leu Pro His 35 40 tac ctg ggc gct ctg gag cgg ctg gac tac ccc cgg gcc agg atg gcc 192 Tyr Leu Gly Ala Leu Glu Arg Leu Asp Tyr Pro Arg Ala Arg Met Ala 50 55 60 ctc tgg tgt gcc acg gac cac. aat gtg gac aac acc aca gag atg ctg 240 Leu Trp Cys Ala Thr Asp His Asn Val Asp Asn Thr Thr Glu Met Leu 65 70 75 288 cag gag tgg ctg gcg gct gtg ggc gat gac tat gct gct-gtg gtc tgg

Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp	
				gag Glu											_	336
				gaa Glu			-							_	-	384
				gcc Ala					-	-			_		_	432
-		_		att Ile	-				_		_				•	480
	-			cca Pro 165			-		_	-	-		_			528
				tgg Trp	_					_				-	•	576
				ttc Phe			_		_	_	-			-		624
-	-		_	gtc Val						-		_		-	-	672
	-	-	_	ctt Leu	_			_								720
		_	-	atc Ile 245		-		_		-	-	-	-	-		768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	999	tac	atg	aat	gtg	816

Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
					cag Gln		_	-	-			-				864
				_	gca Ala			_			-	-	-	-		912
					ccc Pro 310											960
					agc Ser											1008
					tgg Trp											1056
					atg Met											1104
				-	ggc Gly		-						_		-	1152
					ggc Gly 390	-			-						•	1200
					ggc Gly											1248
					aac Asn		Arg									1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

**5**0

Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440	Trp	Asp	Leu	Ile	Tyr 445	Leu	Gly	Arg	
					gag G1u											1392
					tac Tyr 470											1440
	-			-	aag Lys	_	_	_		-		_	-	-	-	1488
-			-		ttc Phe	-			_		_	-				1536
	_		_	_	cac His					-	_		-			1584
					gct Ala											1632
		-	-	_	gag Glu 550						_	-	-	-		1680
_			_		agc Ser				_		_	_	-		•	1728
tgg Trp	acc Thr	tga *														1737

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<211> 578

<212> PRT

<213> Homo sapiens

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Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
        355
                            360
                                                365
Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
    370
                                            380
                        375
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
                   390
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
                                425
Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
                            440
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
                        455
                                            460
Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
                    470
                                        475
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
                                    490
                485
Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
                                505
                                                    510
Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
        515
                            520
                                                525
Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
    530
                        535
                                            540
Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Ser Gly
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Arg Leu Ile Ser Trp Ser Gly Ser Gln Lys Thr Leu Arg Ser Pro Ala
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Trp Thr
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<211> 1152

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(1152)

<400> 33

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96		gca Ala														
144		cat His														
192	_	gca Ala	-		-	-	-	-								
240	•	cag Gln	-		Ψ.		_	_		~		•	•	_		
288	_	att Ile 95					_		-				_	-	-	
336	-	ttg Leu				-	-		_	-	-			_	-	
384		aga Arg					_	-	-	-	_	_	_			
432		agc Ser	_		-				_	_			-			
480	-	cca Pro				_			_						-	-
528		atg Met 175				-				-	_		_			
. 576	gtc	gca	att	gaa	ggt	aaa	ttt	gaa	gaa	gca	atg	gga	ctt	gtg	tat	atg

Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	Glu 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val		
						aca Thr							_	_	_		624
_						gaa Glu 215	_	-					-				672 <sup>-</sup>
-	_	_	-			att Ile			_			_					720
						aat Asn											768
	_			-		aaa Lys					-			-			816
		-	-			gaa Glu	_	_	-	_			-				864
	-			_		aaa Lys 295	-			_	_	_					912
	-			-		gaa Glu	-			-		•	-	-			960
	_	-	-	-	-	aaa Lys	_			-			_		-	1	800
						ggc Gly	_								_	1	056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1	104

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 atg agt atg act act gat gac ttt gta aaa atg ttt tca ggg aac taa 1152 Met Ser Met Thr Thr Asp Asp Phe Val Lys Met Phe Ser Gly Asn \* 370 375 <210> 34 <211> 383 <212> PRT <213> Homo sapiens <400> 34 Met Leu Pro Asn Thr Gly Arg Leu Ala Gly Cys Thr Val Phe Ile Thr Gly Ala Ser Arg Gly Ile Gly Lys Ala Ile Ala Leu Lys Ala Ala Lys 25 Asp Gly Ala Asn Ile Val Ile Ala Ala Lys Thr Ala Gln Pro His Pro Lys Leu Leu Gly Thr Ile Tyr Thr Ala Ala Glu Glu Ile Glu Ala Val 55 60 Gly Gly Lys Ala Leu Pro Cys Ile Val Asp Val Arg Asp Glu Gln Gln Ile Ser Ala Ala Val Glu Lys Ala Ile Lys Lys Phe Gly Gly Ile Asp 90 Ile Leu Val Asn Asn Ala Ser Ala Ile Ser Leu Thr Asn Thr Leu Asp 100 105 Thr Pro Thr Lys Arg Leu Asp Leu Met Met Asn Val Asn Thr Arg Gly 120 Thr Tyr Leu Ala Ser Lys Ala Cys Ile Pro Tyr Leu Lys Lys Ser Lys 135 Val Ala His Ile Leu Asn Ile Ser Pro Pro Leu Asn Leu Asn Pro Val 150 155 Trp Phe Lys Gln His Cys Ala Tyr Thr Ile Ala Lys Tyr Gly Met Ser 170 165 Met Tyr Val Leu Gly Met Ala Glu Glu Phe Lys Gly Glu Ile Ala Val 185 Asn Ala Leu Trp Pro Lys Thr Ala Ile His Thr Ala Ala Met Asp Met 200 Leu Gly Gly Pro Gly Ile Glu Ser Gln Cys Arg Lys Val Asp Ile Ile 215 220 Ala Asp Ala Ala Tyr Ser Ile Phe Gln Lys Pro Lys Ser Phe Thr Gly 225 230 235 240

Asn	Phe	Val	Ile	Asp 245	Glu	Asn	Пe	Leu	Lys 250	Glu	Glu	Gly	He	G1u 255	Asn	
Phe	Asp	Val	Tyr 260	Ala	Пe	Lys	Pro	Gly 265	His	Pro	Leu	Gln	Pro 270	Asp	Phe	
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	Ala 280	Val	Ser	Lys	Lys	Va1 285	Glu	Ser	Thr	
Gly	Ala 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys		G1n 300	Leu	Gln	Pro	Lys	
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315	Ile	Val	Lys	Asp	Ser 320	
Leu	Ser	Asp ·	Asp	Va1 325	Val	Lys	Ala	Thr	G1n 330	Ala	Ile	Tyr	Leu	Phe 335	Glu	
	Ser	_	340	Ÿ	·			345			·		350			
	Gly	355			·	•	360			•		365	·		Val	
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn		
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	tgc Cys								-						-	
-	aac Asn				_	-									_	144

gtg Val 50											192
tac Tyr	_	_		 _	 	 -					240
ctg Leu											288
tac Tyr				_	 -						336
ctc Leu							-	-	-		384
aat Asn 130				_	_	_					432
ggt Gly											480
ttc Phe		_	 					•	_	-	528
ctc Leu											576
gag Glu			-								624
ctc Leu 210											672

		ccc Pro 230					_	_			720
		ttc Phe							_	_	768
		gcc Ala				_	_	-	-	_	816
		acc Thr	_	-			-	Leu		•	864
		tgc Cys					-	-			912
		ggc Gly 310			-		-			-	960
		 ggc Gly				-	_				1008
		tca Ser							-	_	1056
		cct Pro									1104
		gag Glu		 -	-			_	_		1152
		tcc Ser 390			_	_		_	-		1200

59

ctg cac gtc atg atg acg ctc acc aac tgg tac aag ccc ggt gag acc 1248 Leu His Val Met Met Thr Leu Thr Asn Trp Tyr Lys Pro Gly Glu Thr 410 405 415 1296 cgg aag atg atc agc acg tgg acc gcc gtg tgg gtg aag atc tgt gcc Arg Lys Met Ile Ser Thr Trp Thr Ala Val Trp Val Lys Ile Cys Ala 420 425 430 agc tgg gca ggg ctg ctc ctc tac ctg tgg acc ctg gta gcc cca ctc 1344 Ser Trp Ala Gly Leu Leu Leu Tyr Leu Trp Thr Leu Val Ala Pro Leu 435 440 ctc ctg cgc aac cgc gac ttc agc tga - 1371 Leu Leu Arg Asn Arg Asp Phe Ser \* 450 455 <210> 36 <211> 456 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(456) <223> Xaa = Any Amino Acid <400> 36 Met Gly Ala Cys Leu Gly Ala Cys Ser Leu Leu Ser Cys Ala Ser Cys Leu Cys Gly Ser Ala Pro Cys Ile Leu Cys Ser Cys Cys Pro Ala Ser 25 Arg Asn Ser Thr Val Ser Arg Leu Ile Phe Thr Phe Phe Leu Phe Leu Gly Val Leu Val Ser Ile Ile Met Leu Ser Pro Gly Val Glu Ser Gln 55 60 Leu Tyr Lys Leu Pro Trp Val Cys Glu Glu Gly Ala Gly Ile Pro Thr 70 75 Val Leu Gln Gly His Ile Asp Cys Gly Ser Leu Leu Gly Tyr Arg Ala 90 Val Tyr Arg Met Cys Phe Ala Thr Ala Ala Phe Phe Phe Phe Thr 105 Leu Leu Met Leu Cys Val Ser Ser Ser Arg Asp Pro Arg Ala Ala Ile

		115					120					125			
Gln	Asn 130	Gly	Phe	Trp	Phe	Phe 135	Lys	Phe	Leu	He	Leu 140	Val	Gly	Leu	Thr
Val 145	Gly	Ala	Phe	Tyr	Ile 150		Asp	Gly	Ser	Phe 155	Thr	Asn	Ile	Trp	Phe 160
Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	Ile	Leu	Ile	Gln	Leu 175	Val
Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185	Asn	Gln	Arg	Trp	Leu 190	Gly	Lys
Ala	Glu	G1u 195	Cys	Asp	Ser	Arg	A1a 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
Thr	Leu 210	Leu	Phe	Tyr	Leu	Leu 215	Ser	Ile	Ala	Ala	Va1 220	Ala	Leu	Met	Phe
Met 225	Tyr	Tyr	Thr	Glu	Pro 230	Ser	Gly	Cys	His	G1u 235	Gly	Lys	٧a٦	Phe	Ile 240
Ser	Leu	Asn	Leu	Thr 245	Phe	Cys	Val	Cys	Va1 250	Ser	Ile	Ala	Ala	Val 255	Leu
			260	Asp				265		•			270		
Val	He	Thr 275	Leu	Tyr	Thr	Met	Phe 280	Val	Thr	Trp	Ser	A1 a 285	Leu	Ser	Ser
He	Pro 290	Glu	Gln	Lys	Cys	Asn 295	Pro	His	Leu	Pro	Thr 300	Gln	Leu	Gly	Asn
305				Ala	310				•	315				•	320
Ala	Pro	Ser	Ile	Va1 325	Gly	Leu	Пe	Пe	Phe 330	Leu	Leu	Cys	Thr	Leu 335	Phe
Ile	Ser	Leu	Arg 340	Ser	Ser	Asp	His	Arg 345	Gln	Val	Asn	Ser	Leu 350	Met	Gln
Thr	Glu	G1u 355	Cys	Pro	Pro	Met	Leu 360	Asp	Ala	Thr	Xaa	G1n 365	Gln	Gln	Gln
	370			Cys		375				-	380			•	
Va1 385	Thr	Tyr	Ser	Tyr	Ser 390	Phe	Phe	His	Phe	Cys 395	Leu	Val	Leu	Ala	Ser 400
Leu	His	Val	Met	Met 405	Thr	Leu	Thr	Asn	Trp 410	Tyr	Lys	Pro	Gly	G1u 415	Thr
Arg	Lys	Met	Ile 420	Ser	Thr	Trp	Thr	A1a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
Ser	Trp	A1a 435	Gly	Leu	Leu	Leu	Tyr 440	Leu	Trp	Thr	Leu	Va1 445	Ala'	Pro	Leu
Leu	Leu 450	Arg	Asn	Arg	Asp	Phe 455	Ser					*			

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61

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62

	130					135					140					
-	-					atc Ile	_			_					•	480
						gct Ala										528
_					-	gca Ala	-	-				_		-	-	576
	-					aca Thr	-						_	-	-	624
_						gaa Glu 215	_	_	_							672
_	-	-	-			att Ile			-							720
				-	-	aat Asn				-	-			-		768
						aaa Lys										816
		-	-			gaa Glu	-	-	-	-			_			864
	_	_		-		aaa Lys 295	-			-	-	-				912
	_			-		gaa G1u	-			_			_	-		960

63

305	310	315	320
	•	caa gca atc tat ctg Gln Ala Ile Tyr Leu 330	•
		ttt ctt gat ctg aaa Phe Leu Asp Leu Lys 350	
		tct gat cag gca gat Ser Asp Gln Ala Asp 365	
		aaa atg ttt tca ggg Lys Met Phe Ser Gly 380	
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		cta atg aat cag atg Leu Met Asn Gln Met 410	_
aga ctg tga Arg Leu *			1257

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<211> 418

<212> PRT

<213> Homo sapiens

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	50					55					60				
Gly 65	Gly	Lys	Ala	Leu	Pro 70	Cys	Пe	Val	Asp	Val 75	Arg	Asp	Glu	Gln	Glr 80
Пe	Ser	Ala	Ala	Va1 85	Glu	Lys	Ala	Ile	Lys 90	Lys	Phe	Gly	Gly	Ile 95	Asp
Пe	Leu	Val	Asn 100	Asn	Ala	Ser	Ala	Ile 105	Ser	Leu	Thr	Asn	Thr 110	Leu	Asp
Thr	Pro	Thr 115	Lys	Arg	Leu	Asp	Leu 120	Met	Met	Asn	Val	Asn 125	Thr	Arg	Gly
Thr	Tyr 130	Leu	Ala	Ser	Lys	Ala 135	Cys	Ile	Pro	Tyr	Leu 140	Lys	Lys	Ser	Lys
Val 145	Ala	His	Ile	Leu	Asn 150	Пе	Ser	Pro	Pro	Leu 155	Asn	Leu	Asn	Pro	Val 160
Trp	Phe	Lys	Gln	His 165	Cys	Ala	Tyr	Thr	Ile 170	Ala	Lys	Tyr	Gly	Met 175	Ser
Met	Tyr	۷a٦	Leu 180	Gly	Met	Ala	Glu	Glu 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val
Asn	Ala	Leu 195	Trp	Pro	Lys	Thr	Ala 200	Ile	His	Thr	Ala	A1a 205	Met	Asp	Met
Leu	Gly 210	Gly	Pro	Gly	Ile	Glu 215	Ser	Gln	Cys	Arg	Lys 220	Val	Asp	Ile	Πe
225	·			•	230					235			Phe		240
				245					250				Ile	255	
	•		260			•		265					Pro 270	·	
		275		•			280					285	Glu		
Ť	290					295					300		Gln		
305					310					315			Lys		320
				325					330				Leu	335	
	•		340			_		345					Lys 350		
		355					360					365	Asp		
	370				•	375			•		380		G1y		
385					390					395			Lys		400
Met	Ala	Leu	Ala	He	Lys	Leu	Glu	Lys	Leu	Met	Asn	Gln	Met	Asn	Ala

65 ·

405 410 415 Arg Leu <210> 39 <211> 627 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(627) <400> 39 atg gtg ttc tac ttc acc agc agc gtt aat tca tct gcc tac act 48 Met Val Phe Tyr Phe Thr Ser Ser Ser Val Asn Ser Ser Ala Tyr Thr 5 1 10 15 att tac atg gga aaa gat aaa tat gaa aat gaa gat ctg atc aag cat 96 Ile Tyr Met Gly Lys Asp Lys Tyr Glu Asn Glu Asp Leu Ile Lys His 20 ggc tgg cct gaa gat atc tgg ttt cat gtg gac aaa ctc tct tcg gct 144 Gly Trp Pro Glu Asp Ile Trp Phe His Val Asp Lys Leu Ser Ser Ala 35 cat gta tac ctt cga tta cat aag gga gag aat ata gaa gac atc cca 192 His Val Tyr Leu Arg Leu His Lys Gly Glu Asn Ile Glu Asp Ile Pro 50 55 aag gaa gtg ctg atg gac tgt gcc cac ctt gtg aag gcc aat agc att 240 Lys Glu Val Leu Met Asp Cys Ala His Leu Val Lys Ala Asn Ser Ile 65 70 75 80 caa ggc tgc aag atg aac aac gtt aat gtg gta tat acg ccg tgg tct 288 Gln Gly Cys Lys Met Asn Asn Val Asn Val Val Tyr Thr Pro Trp Ser aac ctg aag aaa aca gct gac atg gat gtg ggg cag ata ggc ttt cac 336 Asn Leu Lys Lys Thr Ala Asp Met Asp Val Gly Gln Ile Gly Phe His 100 105 110 384 agg cag aag gat gta aaa att gtg aca gtg gag aag aaa gta aat gag Arg Gln Lys Asp Val Lys Ile Val Thr Val Glu Lys Lys Val Asn Glu

	66															
		115					120					125				
						aag Lys 135										432
				-	-	aga Arg	_	_	-							480
						aaa Lys										528
						ctt Leu							_		_	576
						cag Gìn										624
taa *																627
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<212> PRT

<213> Homo sapiens

<400> 40

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				85					90					95		
Asn	Leu	Lys	Lys 100	Thr	Ala	Asp	Met	Asp 105	Val	Gly	Gln	Пe	Gly 110	Phe	His	
Arg	Gln	Lys 115	Asp	Val	Lys	Ile	Val 120	Thr	Val	Glu	Lys	Lys 125	Val	Asn	Glu	
He	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	۷al	Glu	Arg 140	Phe	Pro	Asp	Leu	
Ala 145	Ala	Glu	Lys	Glu	Cys 150	Arg	Asp	Arg	Glu	Glu 155	Arg	Asn	Glu	Ļys	Lys 160	
Ala	Gln	Ile	Gln	Glu 165	Met	Lys	Lys	Arg	G1u 170	Lys	Glu	Glu	Met	Lys 175	Lys	
Lys	Arg	Glu	Met 180	Asp	Glu	Leu	Arg	Ser 185	Tyr	Ser	Ser	Leu	Met 190	Lys	Val	
Glu	Asn	Met 195	Ser	Ser	Asn	Gln	Asp 200	Gly	Asn	Asp	Ser	Asp 205	Glu	Phe	Met	
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	<2	222>	(1).	(4	ature 174) .C or											
		<b>100&gt;</b>														
											ctg Leu					. 48
										_	gtc Val	-				. 96
											nag Xaa					144
											999 Gly					192

68

50 55 60 ccc cag tgc ggc ttc agc aac gcc gtg gtg cag atc ctg cgg ctg cac 240 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 65 70 75 ggc gtc cgc gat tac gcg gcc tac aac gtg ctg gac gac ccg gag ctc 288 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 85 cga caa ggc att aaa gac tat tcc aac tgg ccc acc atc ccg caa gtg 336 Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 100 105 110 tac ctc aat ggc gag ttt gta ggg ggc tgt gac att ctt ctg cag atg 384 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 115 120 125 cac cag aat ggg gac ttg gtg gaa gaa ctg aaa aag ctg ggg atc cac 432 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 130 135 tcc gcc ctt tta gat gaa aag aaa gac caa gac tcc aag tga 474 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys \* 145 150 155. <210> 42 <211> 157 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(157) <223> Xaa = Any Amino Acid <400> 42 Met Ser Gly Ser Leu Gly Arg Ala Ala Ala Leu Leu Arg Trp Arg 10 Leu Cys Ala Gly Gly Gly Leu Trp Gly Pro Val Val Arg Thr Ala 25 Gly Ser Ala Pro Gly Gly Gly Gly Ser Ala Xaa Xaa Leu Asp Ala Leu 45 35 40

Val Lys Lys Asp Lys Val Val Val Phe Leu Lys Gly Thr Pro Glu Gln 50 55 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 70 75 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 90 . Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 105 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 120 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 135 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys 145 150 155 <210> 43 <211> 1032 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1032) <400> 43 48 Met Gly Gly Pro Arg Gly Ala Gly Trp Val Ala Ala Gly Leu Leu Leu 1 10 ggc gcg ggc gcc tgc tac tgc att tac agg ctg acc cgg ggt cgg cgg 96 Gly Ala Gly Ala Cys Tyr Cys Ile Tyr Arg Leu Thr Arg Gly Arg Arg 20 25 cgg ggc gac cgc gag ctc ggg ata cqc tct tcg aag tcc gca ggt qcc 144 Arg Gly Asp Arg Glu Leu Gly Ile Arg Ser Ser Lys Ser Ala Gly Ala 35 40 45 ctg gaa gaa ggg acg tca gag ggt cag ttg tgc ggg cgc tcg gcc cgg 192 Leu Glu Glu Gly Thr Ser Glu Gly Gln Leu Cys Gly Arg Ser Ala Arg 50 55 cct cag acg gga ggt acc tgg gag tca cag tgg tcc aag acc tcg cag 240 Pro Gln Thr Gly Gly Thr Trp Glu Ser Gln Trp Ser Lys Thr Ser Gln 65 70 75 80

	-	-			_				•	-			aat Asn	-	-	288
		_					-	_			-		gat Asp 110		_	336
		-	-	-	-			_				-	gcc Ala			384
_			-			_	_	_					att Ile	_	_	432
							-						gct Ala			480
					Ser			-	-				aag Lys		_	528
					-	-							cct Pro 190	_		576
			-	_	-		-		_	_			atg Met		-	624
						-			-				gac Asp	-		672
									-				gtt Val	-		720
_		_		_		_			-	_		_	gga Gly			768

													agc Ser 270		-	816
-	-					-	-						aat Asn		-	864
	-				_					-			act Thr			912
_			_			_				-	-	_	gcc Ala	-		960
													gaa Glu	_	-	1008
-	aca Thr						tga *									1032
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Gly	Ala	Gly	A1 a 20		Tyr	Cys	Ile	Tyr 25		Leu	Thr	Arg	Gly 30	Arg	Arg	
Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40	Arg	Ser	Ser	Lys	Ser 45	Ala	Gly	Ala	
Leu	Glu 50		Gly	Thr	Ser	G1u 55		Gln	Leu	Cys	Gly 60		Ser	Ala	Arg	
Pro 65		Thṛ	Gly	Gly	Thr 70	-	Glu	Ser	Gln	Trp 75		Lys	Thr	Ser	G1n 80	
	Glu	Asp	Leu	Thr		Gly	Ser	Tyr	Asp		۷a٦	Leu	Asn	Ala		

95

Gln Leu Gln	Lys Leu 100	Leu Ty	r Leu	Leu 105	Glu	Ser	Thr	Glu	Asp 110	Pro	Val
Ile Ile Glu . 115		Leu I	e Thr 120		Gly	Asn	Asn	Ala 125		Phe	Ser
Val Asn Gln . 130	Ala Ile		rg Glu 85		Gly	Gly	Ile 140	Pro	Ile	Val	Ala
Asn Lys Ile 1 145	•	150				155					160
Ala Leu Asn	165				170					175	
	180	_		185				_	190		
Ser Ala Val			200					205			
Thr Asn Asp 1		21	.5				220				
Gln Val Leu   225		230	_			235					240
Leu Leu Leu	245				250				_	255	
	260			265				·	270		
			280					285			
Asn Cys Leu 1 290		29	5				300				
Glu Gly Ser I 305	Leu Phe	Phe Le	u Leu	His	Gly	G1u 315	Glu	Cys	Ala	Gln	Lys 320
Ile Arg Ala I	Leu Val 325	Asp Hi	s His	Asp	Ala 330	Glu	Val	Lys	Glu	Lys 335	Val
Val Thr Ile	Ile Pro 340	Lys Il	e								
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	misc_fea										
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<223> n = A.T.C or G

WO 01/29221

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74

Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu	
				tgg Trp		_	-					_	_		_	576
		-		gca Ala		_		_				-	_			624
_			-	cat His				-								672
				acc Thr												720
		_	-	atc Ile 245		_	_		-			_	_		-	768
-			_	ttg Leu				_		-	-	-		-	-	816
		-		gac Asp			-					-		_		864
			_	att Ile				-		-			-		-	912
-				ttg Leu		_			_							960
				ttc Phe 325											_	1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

Phe Thr Val Phe Gly Gly Leu N 340	Met Ala Phe Asn Tyr Asn Arg Ala Phe 345 350	
Gln Val Trp Ala Val Pro Leu L	tta ttg gta gct ttt ttt gcc tac tta Leu Leu Val Ala Phe Phe Ala Tyr Leu 360 365	1104
	gtg ttt gaa act gtg ctg gat gca ctt Val Phe Glu Thr Val Leu Asp Ala Leu 380	1152
	ctg gaa aca aat gat gga tcg tca gaa Leu Glu Thr Asn Asp Gly Ser Ser Glu 395 400	1200
	gaa ttt ctg agt ttc gta aaa agg agc Glu Phe Leu Ser Phe Val Lys Arg Ser 410 415	1248
, , ,	gca cag cag gac aag cac tca tta agg Ala Gln Gln Asp Lys His Ser Leu Arg 425 430	1296
aat gag gag gga aca gaa ctc d Asn Glu Glu Gly Thr Glu Leu G 435		1335
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Leu Ser Leu Ala Met Met Phe T 20	Thr Phe Arg Phe Ile Thr Thr Leu Leu 25 30	
Val His Ile Phe Ile Ser Leu V	Val Ile Leu Gly Leu Leu Phe Val Cys	

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Пe
G1u 65	Leu	Asp	Thr	Glu	Arg 70	Glu	Asn	Met	Lys	Cys 75	Val	Leu	Gly	Phe	Ala 80
Пe	Val	Ser	Thr	G1y 85	Ile	Thr	Ala	Val	Leu 90	Leu	Val	Leu	He	Phe 95	Val
Leu	Arg	Lys	Arg 100	Ile	Lys	Leu	Thr	Val 105	Glu	Leu	Phe	Gln	Ile 110	Thr	Asn
Lys	Ala	Ile 115	Ser	Ser	Ala	Pro	Phe 120	Leu	Leu	Phe	Gln	Pro 125	Leu	Trp	Thr
Phe	Ala 130	Ile	Leu	Ile	Phe	Phe 135	Trp	Val	Leu	Trp	Val 140	Ala	Val	Leu	Leu
Ser 145	Leu	Gly	Thr	Ala	Gly 150	Ala	Ala	Gln	Val	Met 155	Glu	Gly	Gly	Gln	Val 160
Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Пе	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu
Ile	Gly	Leu	Ile 180	Trp	Thr	Ser	Glu	Phe 185	Ile	Leu	Ala	Cys	Gln 190	Gln	Met
		195					200			Phe		205			
	210					215				Leu	220				
Tyr 225	His	Gln	Gly	Thr	11e 230	Val	Lys	Gly	Ser	Phe 235	Leu	Ile	Ser	Val	Va1 240
Arg	Ile	Pro	Arg	11e 245	IJе	Val	Met	Tyr	Met 250	Gln	Asn	Ala	Leu	Lys 255	Glu
			260					265		Arg			270		•
		275		•	•	·	280			Leu		285			
	290					295				Cys	300				•
Ala 305	Phe	Lys	Ile	Leu	Ser 310	Lys	Asn	Ser	Ser	His 315	Phe	Thr.	Ser	Пe	Asn 320
Cys	Phe	Gly	Asp	Phe 325	Ile	Пе	Phe	Leu	Gly 330	Lys	Val	Leu	Val	Va1 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Va1	Ala	Phe	Phe 365	Ala	Tyr	Leu
Val	Ala 370	His	Ser	Phe	Leu	Ser 375	Val	Phe	Glu	Thr	Val 380	Leu	Asp	Ala	Leu
Phe	Leu	Cvs	Phe	Ala	Val	Asn	Leu	Glu	Thr	Asn	Asn	Glv	Ser	Ser	Glu

385					390					395					400	
				405	·				410				Lys	415		
			420			_		425		·		His	Ser 430	Leu	Arg	
Asn	Glu	G1u 435	Gly	Thr	Glu	Leu	G1n 440	Ala	Ile	Val	Arg					
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													gga Gly 30		-	96
			_	_		_			_				gga Gly	_		144
													tta Leu			192
-	-			-		-				_	-		aag Lys			240
								-				-	ctt Leu	_	-	288
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78

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				gaa Glu	-	_	_		-		_		14	4
				gaa Glu 55									19	2
				gtg Val									24	0
		_	_	gcc Ala	_					_	-		28	8
				acc Thr									33	6
				tgt Cys									38	4
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Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

-	-	_			-	aag Lys				-				•	144
-				_	-	gat Asp 55				_				-	192
		-				gaa Glu					-	-	-		240
	-		_	_		aca Thr	_	-	-	-	-			-	288
	_				-	cct Pro	-	-						_	336
	-				-	gtt Val		Glu			-		-		384
					_	ctg Leu 135								-	432
						ctg Leu	-							-	480
						gag G1u									528
						gag Glu									576
				_		gac Asp			_						624

82

		_		cag Gln						-	-	•	•	672
				agc Ser 230								_	_	720
-	_	_	_	tgc Cys		-		-	-	_				768
				cac His	-	-							-	816
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ccg Pro	tga *													870

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 Met
 Pro
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 Lys
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 Val
 His
 Gly
 Ser
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 Phe
 Gly
 Glu
 Gly
 Fro
 Val
 Phe
 Arg
 Arg
 Arg
 Arg
 Arg
 Ser
 Phe
 Leu
 Lys
 Arg
 Leu
 Arg
 Arg
 Leu
 Leu
 Lys
 Arg
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 Leu
 Lys
 Arg
 Leu
 Leu
 Lys
 Arg
 Leu
 Tyr
 Phe
 Leu
 Lys
 Arg
 Leu
 Tyr
 Tyr</th

83

100 105 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro 120 Lys Gly Lys Lys Phe Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys 140 130 135 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly, Arg 150 155 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly 165 170 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys 180 185 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 200 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys · 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 230 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His 275 280 285 Pro <210> 53 <211> 1041 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1041) <221> misc feature <222> (1)...(1041) <223> n = A.T.C or G<400> 53 48 Met Pro Arg Val Phe Val Phe Arg Ala Leu Leu Val Leu Ile Phe

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	_	_						-	-	atc Ile 60		-	_			192
		_	-	_	_		_	_	_	gtg Val	_	-				240
_				_		-				ctg Leu						288
_	_	_		_	_					gat Asp						336
					_				-	gca Ala	_			_		384
-		-		-		_	-			agt Ser 140						432
										cgg Arg						480
										cat His						528
										gaa Glu						576

			cag G1n									_	624
		-	gag Glu	_	_						_	_	672
			tac Tyr 230	_	_				_	_		cac His 240	720
			ctg Leu			_	-		-				768
	_	-	ttc Phe		-				_				816
			gac Asp									-	864
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Ser	Asp 290	Glu	Ala	Val	Thr	Asn 295	Gly	Leu	Arg	Asp	G1y 300	IJе	Val	Phe	Val	
Leu 305	Lys	Cys	Leu	Asp	Phe 310	Ser	Leu	Val	Val	Asn 315	Val	Lys	Lys	Ile	Pro 320	
Phe	Ile	Ile	Leu	Ser 325	Glu	Glu	Phe	Ile	Asp 330	Pro	Lys	Ser	His	Lys 335	Phe	
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•	Ala	Gly	Ser 20		Arg	Gly	His	G1 <i>y</i> 25		Ser	Arg	Glu	Thr 30		G1n	
Glu	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Thr	Arg	Ala 45	Asn	His	Asn	
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													Val	_		40
													gag Glu 30		-	96
													cac His			144
													gaa Glu		_	192
						_			-	-			ctg Leu		-	240
										-			ctc Leu		-	288

										_			tgg Trp		336
						_			•	-	•		gtt Val		384
									-				ttg Leu	_	432
											-		ggc Gly		480
-			_	_	-	_							tta Leu 175		528
	_				-	-	-	_	-				ctt Leu		576
							-	-	-	-		-	gaa Glu	-	624
		-		_	-						-		tcg Ser		672
													999 Gly		720
							-						acg Thr 255		768
agg Arg						-						-	ggc Gly		816

WO 01/29221

_			_	_		_	-		_		 aag Lys	_	864
-	-		_		_			 			gtc Val	_	912
		_	_	-			_	-	_	-	 cag Gln		960
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90

PCT/US00/29052

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<213> Homo sapiens

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115

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120

Phe	Arg 130	Ala	Thr	Arg	Lys	Pro 135	Leu	Val	Gln	Thr	Thr 140	Pro	Arg	Leu	Val		
Tyr 145	Lys	Trp	Phe	Leu	Leu 150	Ile	Tyr	Lys	Ile	Ser 155	Tyr	Ala	Thr	Gly	Ile 160		
Val	Gly	Tyr	Met	Ala 165	Val	Met	Phe	Thr	Leu 170	Phe	Gly	Leu	Asn	Leu 175	Leu		
Phe	Lys	Пе	Lys 180	Pro	Glu	Asp	Ala	Met 185	Asp	Phe	Gly	Ile	Ser 190	Leu	Leu		
Phe	Tyr	Gly 195	Leu	Tyr	Tyr	Gly	Val 200	Leu	Glu	Arg	Asp	Phe 205	Ala	Glu	Met		
Cys	Ala 210	Asp	Tyr	Met	Ala	Ser 215	Thr	Пe	Gly	Phe	Tyr 220	Ser	Glu	Ser	Gly		
Met 225	Pro	Thr	Lys	His	Leu 230	Ser	Asp	Ser	Val	Cys 235	Ala	Val	Cys	Gly	G1n 240	•	
Gln	Пe	Phe	Val	Asp 245	Val	Ser	Glu	Glu	Gly 250	Пe	He	Glu	Asn	Thr 255	Tyr		
_			260	Asn				265					270		•		
		275	·	Lys			280			•	·	285					
·	290			Met		295					300						
305				Leu	310	•		_		315					320		
Val	Ile	Ile	Gly	Val 325	Val	Gln	Gly	Ile	Asn 330	Tyr	Ile	Leu	Gly	Leu 335	Glu		
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				cag Gln 5													48

					ggc Gly					-				_	-		96
_					act Thr	-		_		_						:	144
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	-			-	agt Ser 70			-		-					_	;	240
		_	_	-	agc Ser	_		_	_	_	-	_	_	-		i	288
					ctg Leu											;	336
					aag Lys											;	384
	agc Ser 130	tag *							•							;	393
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		35					40					45					
_		_	_		_	_	-			tcc Ser				_	_		192
			_	_				-	-	tta Leu 75			-				240
								-		caa G1n			-				288
		-		-		-	_		-	caa G1n	_						336
_		-			-				_	cca Pro	_			-	-		384
					_			_		att Ile		-	-		ctc Leu	•	432
		-		_			-			aaa Lys 155					-		480
	-			Phe		Gly	Leu	Ala	Ile	999 Gly	Thr	Leu					528
										gga Gly						٠	576
-	_		-		_	_	-	_		ttt Phe							624
					-	_		_	-	tta Leu							672

210					215					220					
Asn				cac His 230		-								•	720
				aaa Lys										-	768
				gtc Val		-	-							_	816
				tct Ser									-		864
			-	999 Gly			_		-			-		-	912
				tgc Cys 310	_	-						-		_	960
				tgc Cys		-				_			-		1008
	-	Пe	Leu	tgt Cys	Glu	Glu	Phe	Pro					Asp		1056
				gca Ala		-						_			1104
			-	tgt Cys		_		-			-				1152
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96

385 390 395 400 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 405 410 415 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc 1296 Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 420 425 430 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 445 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa 1383 Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu \* 450 455 460 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 10 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu 40 Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro 55 60 Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 70 -75 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 100 105 110

Cys	Glu	Asp 115	Arg	Pro	Lys	His	Lys 120	Thr	Arg	Pro	Ser	His 125	Ser	Glu	۷a۱
Trp	Gly 130	Tyr	Gly	Phe	Leu	Ser 135	Val	Thr	IJе	Пe	Asn 140	Leu	Ala	Ser	Leu
Leu 145	Gly	Leu	Ile	Leu	Thr 150	Pro	Leu	Ile	Lys	Lys 155	Ser	Tyr	Phe	Pro	Lys 160
Пe	Leu	Thr	Phe	Phe 165	Val	Gly	Leu	Ala	Ile 170	Gly	Thr	Leu	Phe	Ser 175	Asn
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Asp	Ser	Tyr 195	Val	Glu	Lys	Ala	Val 200	Ala	Val	Phe	Gly	Gly 205	Phe	Tyr	Leu
Leu	Phe 210	Phe	Phe	Glu	Arg	Met 215	Leu	Lys	Met	Leu	Leu 220	Lys	Thr	Tyr	Gly
G1n 225	Asn	Gly	His	Thr	His 230	Phe	Gly	Asn	Asp	Asn 235	Phe	Gĺy	Pro	Gln	G1u 240
Lys	Thr	His	Gln	Pro 245	Lys	Ala	Leu	Pro	Ala 250	Ile	Asn	Gly	Val	Thr 255	Cys
Tyr	Ala	Asn	Pro 260	Ala	Val	Thr	Glu	A1a 265	Asn	Gly	His	Ile	His 270	Phe	Asp
Asn	Val	Ser 275	Val	Val	Ser	Leu	G1n 280	Asp	Gly	Lys	Lys	G1u 285	Pro	Ser	Ser
Cys	Thr 290	Cys	Leu	Lys	Gly	Pro 295	Lys	Leu	Ser	Glu	Ile 300	Gly	Thr	Ile	Ala
Trp 305	Met	Ile	Thr	Leu	Cys 310	Asp	Ala	Leu	His	Asn 315	Phe	Ile	Asp	Gly	Leu 320
Ala	Ile	Gly	Ala	Ser 325	Cys	Thr	Leu	Ser	Leu 330	Leu	Gln	Gly	Leu	Ser 335	Thr
Ser	He	Ala	Ile 340	Leu	Cys	Glu	Glu	Phe 345	Pro	His	Glu	Leu	Gly 350	Asp	Phe
Val	He	Leu 355	Leu	Asn	Ala	Gly	Met 360	Ser	Thr	Arg	Gln	A1a 365	Leu	Leu	Phe
Asn	Phe 370		Ser	Ala	Cys	Ser 375	-	Tyr	Val	Gly	Leu 380		Phe	Gly	Пe
Leu 385	Val	Gly	Asn	Asn	Phe 390	Ala	Pro	Asn	Ile	Ile 395	Phe	Ala	Leu	Ala	Gly 400
Gly	Met	Phe	Leu	Tyr 405	Пe	Ser	Leu	Ala	Asp 410	Met	Phe	Pro	Glu	Met 415	Asn
Asp	Met	Leu	Arg 420	Glu	Lys	Val	Thr	Gly 425	Arg	Lys	Thr	Asp	Phe 430	Thr	Phe
Phe	Met	I1e 435	G1n	Asn	Ala	Gly	Met 440	Leu	Thr	Gly	Phe	Thr 445	Ala	Пe	Leu
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								aca Thr					-		240
-						_	_	gac Asp			-	-	_	•	288
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99

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_		-	_		agg Arg		-								•	192
-			-	-	gag Glu 70		-			_	-			_		240
					cat His									-	_	288
					cct Pro											336
			-	-	ttt Phe		-			_				-		384
					aac Asn										-	432
			-		aag Lys 150		_					-			-	480
					gaa Glu		_			-	_	tga *				519
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Met 1				Val 5	Met	Glu	Val	Trp	His 10 ·	Gly	Leu	Val	Ile	Ala 15	Val	
1/27	Can	1 0	Dha	1	~1~	۸٦.	C	Dha	1	The	۸٦ -	T1.	A	T	1	

Val Ser Leu Phe Leu Gln Ala Cys Phe Leu Thr Ala Ile Asn Tyr Leu

25

30

Leu	Ser	Arg 35	His	Met	Ala	His	Lys 40	Ser	Glu	Gln	Ile	Leu 45	Lys	Ala	Ala	
Ser	Leu 50	Gln	Val	Pro	Arg	Pro 55	Ser	Pro	Gly	His	His 60	His	Pro	Pro	Ala	
Va1 65	Lys	Glu	Met	Lys	G1u 70	Thr	Gln	Thr	G1u	Arg 75	Asp	Ile	Pro	Met	Ser 80	
Asp	Ser	Leu	Tyr	Arg 85	His	Asp	Ser	Asp	Thr 90	Pro	Ser	Asp	Ser	Leu 95	Asp	
Ser	Ser	Cys	Ser 100	Ser	Pro	Pro	Ala	Cys 105	Gln	Ala	Thr	Glu	Asp 110	Val	Asp	
Tyr	Thr	Gln 115	Val	Val	Phe	Ser	Asp 120	Pro	Gly	Glu	Leu	Lys 125	Asn	Asp	Ser	
Pro	Leu 130	Asp	Tyr	Glu	Asn	Ile 135	Lys	Glu	Ile	Thr	Asp 140	Tyr	Val	Asn	Val	
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										tca Ser						96
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										cgg Arg						192

	agc Ser			-										-	_		240
	gac Asp																288
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	cgc Arg				-	_									_	-	384
_	cgc Arg 130	tga *															393
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Gln	Ala	Ile	Cys 20		Leu	Pro	Glu	Arg 25		Ser	Ala	Tyr	Asn 30		Arg		
Ala	G]n	A1a 35		Arg	Leu	Gln	Gly 40		Val	Ala	Gly	Ala 45		G1u	Asp		
Leu	Glu 50	Arg	Ala	Val	Glu	Leu 55	Ser	Gly	Gly	Arg	Gly 60	Arg	Ala	Ala	Arg		
G1n 65	Ser	Phe	Val	Gln	Arg 70		Leu	Leu	Ala	Arg 75	Leu	Gln	Gly	Arg	Asp 80		
	Asp	Ala	Arg	Arg 85		Phe	Glu	Arg	A1a 90		Arg	Leu	Gly	Ser 95			
Phe	Ala	Arg	Arg 100		Leu	Val	Leu	Leu 105		Pro	Tyr	Ala	Ala 110		Cys		
Asn	Arg	Met 115		Ala	Asp	Met	Met 120		Gln	Leu	Arg	Arg 125		Arg	Asp		

Ser	Arg 130														
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													atc Ile		144
				_	_	-		_	-				tta Leu	_	192
		_	-	-				_					ttt Phe	-	240
													gtg Val 95		288
-			_		_	_		_	_				atc Ile		336
	-	_			aac Asn				•	_		taa *			378

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PCT/US00/29052

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Lys	Val	Va1 35	Ser	Gly	Arg	Ile	Ile 40	Asn	Gly	Tyr	Cys	Arg 45	-	Asp	Trp		
	ctg Leu 50													_	-	1	.92
	cta Leu														_	2	240
	acc Thr															2	288
	atc Ile															3	36
	ggg Gly															3	84
	gca Ala 130												-	-		4	32
	acc Thr															4	80
	gac Asp															5	28
	gcc Ala				-	-	_	_		-					_	5	76
	cat His							_		_		-	-	-	-	6	24
aag	acc	cag	ggc	ссс	agc	acg	<b>9</b> 99	ctg	gac	tga						6	57

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Leu Gly Ala Pro Val Glu Gly Glu Ala Lys His Trp Glu Pro Phe Arg
Lys Val Val Ser Gly Arg Ile Ile Asn Gly Tyr Cys Arg Gly Asp Trp
Leu Leu Ser Phe Val Tyr Arg Thr Ser Ser Val Gln Leu His Val Ala
                        55
                                            60
Gly Leu Gln Pro Val Leu Leu Gln Asp Arg Arg Val Glu Asn Val Asp
Leu Thr Ser Val Val Ser Gly His Leu Asp Tyr Ala Lys Gln Met Asp
                85
                                    90
Ala Ile Leu Lys Ala Val Gly Ile Arg Thr Lys Pro Gly Trp Asp Glu
                                105
Lys Gly Leu Leu Ala Pro Gly Cys Leu Pro Ser Glu Glu Pro Arg
                            120
Gln Ala Ala Ala Ala Ser Ser Gly Glu Thr Pro His Gln Val Gly
                       135
Gln Thr Gln Gly Pro Ile Ser Gly Asp Thr Ser Lys Leu Ala Met Ser
                   150
                                        155
Thr Asp Pro Ser Gln Ala Gln Val Pro Val Gly Leu Asp Gln Ser Glu
                                    170
Gly Ala Ser Leu Pro Ala Ala Ala Ser Pro Glu Arg Pro Pro Ile Cys
                                185
Ser His Gly Met Asp Pro Asn Pro Leu Gly Cys Pro Asp Cys Ala Cys
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                                                205
Lys Thr Gln Gly Pro Ser Thr Gly Leu Asp
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								tac Tyr							-	144
					-			aac Asn	-	-	-	_	_			192
								atc Ile					-			240
						-		gtc Val				-		_		288
				-				ctc Leu 105	_	_		-		-	-	336
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Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu Ala Asp Trp Val Cys
                            40
Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Ala Leu Asp Tyr Glu
                        55
Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
                    70
                                        75
Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
                                    90
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
            100
                                105
                                                     110
Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
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                                                125
Arg His His Cys Gln Gly Lys Asp Leu Thr Glu Trp Val Asp Gly Cys
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Asp Phe
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1
                 5
                                     10
                                                          15
acc tgg tcg tca gcc gcc ttc att atc tcc tac gtg gtc gcc qtg ctc
                                                                       96
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Thr	Trp	Ser	Ser 20	Ala	Ala	Phe	Ile	Ile 25	Ser	Tyr	Val	Val	A1a 30	۷a۱	Leu	
			gtc Val					_			_	-	_			144
			gag Glu	_						_					_	192
			gca Ala		-	-			-				-	_	_	240
			acc Thr	-			-			_			•	~ ~		288
			gga Gly 100	Leu												336
	cag G1n	tga *														345
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Met 1		l00> Cys	76 Phe	Leu 5	Arg	Gly	Met	Ala	Phe 10	Val	Pro	Phe	Leu	Leu 15	Val	
Thr	Trp	Ser	Ser 20	Ala	Ala	Phe	Пe	I 1e 25		Tyr	Val	Val	Ala 30		Leu	
		35	Val				40					45		_		
	50		Glu			55		-			60					
Phe 65	Leu	Gly	Ala	Ala	Thr 70	Met	Tyr	Thr	Arg	Tyr 75	Lys	Ile	Val	G1n	Lys 80	

110

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		ttt Phe 115														384
-		aaa Lys			_	_					_		_		_	432
		ctg Leu		-	-	-	_			-	_	-	-		_	480
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		gag Glu			-								-	_	_	576
	_	gtc Val 195		_		_			_					_	~ ~	624
		tca Ser	_		_							_	-	_	_	672
		tac Tyr			_							-		_	•	720
-		tac Tyr	-	_	_		-		-	-		-				768
_		tcc Ser		-		_	-				_	_			-	816
		cac His 275														864

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1		LCu	LCU	5	LCu	741	1113	uij	10		LCu	• • •	1110	15	d i u	
Lys	Phe	Lys	Leu 20	Phe	Thr	Leu	Val	Ser 25	Ala	Cys	Пe	Pro	Va1 30	Phe	Arg	
Leu	Ala	Arg 35	Arg	Arg	Lys	Lys	11e 40	Leu	Phe	Tyr	Cys	His 45	Phe	Pro	Asp	
Leu	Leu 50	Leu	Thr	Lys	Arg	Asp 55	Ser	Phe	Leu	Lys	Arg 60	Leu	Tyr	Arg	Ala	
Pro 65	Ile	Asp	Trp	Ile	G1u 70	Glu	Tyr	Thr	Thr	G1y 75	Met	Ala	Asp	Cys	Ile 80	
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Ser	Leu	Ser	His 100	Ile	Asp	Pro	Asp	Val 105	Leu	Tyr	Pro	Ser	Leu 110	Asn	Val	
Thr	Ser	Phe 115	Asp	Ser	Val	Val	Pro 120	Glu	Lys	Leu	Asp	Asp 125	Leu	Val	Pro	
Lys	Gly 130	Lys	Lys	Phe	Leu	Leu 135	Leu	Ser	Ile	Asn	Arg 140	Tyr	Glu	Arg	Lys	
Lys 145		Leu	Thr	Leu	Ala 150		Glu	Ala	Leu	Val 155	Gln	Leu	Arg	Gly	Arg 160	
	Thr	Ser	Gln	Asp 165		Glu	Arg	Val	His 170		Пe	Val	Ala	Gly 175		
Tyr	Asp	Glu	Arg 180		Leu	Glu	Asn	Val 185		His	Tyr	Gln	G1u 190		Lys	

113

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1 5 10 15

cgn tcc acg gcc gcc gag cta ctg cgc ctg gga gcg cgg gtg atc atg 96 Xaa Ser Thr Ala Ala Glu Leu Leu Arg Leu Gly Ala Arg Val Ile Met

			20					25				30				
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_			-	-	gcc Ala			-					_	_		192
	7	-			ata Ile 70	-						-	_	-	2	240
-		-	-		tgc Cys	_	-	_		-	_			-	2	288
-	-	_			aac Asn	_				_	-		-	-	3	336
					gag G1u	_	-								3	384
					ctt Leu										4	132
-				_	gtt Val 150	Ser		Lys					-		4	180
			-	_	aac Asn	-	-							-	5	528
					ctg Leu										5	576
					aca Thr				-		-				6	524

115

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Gly Val Gly Glu Leu Ile Val Arg Glu Leu Asp Leu Ala Ser Leu Arg
Ser Val Arg Ala Phe Cys Gln Glu Met Leu Gln Glu Glu Pro Arg Leu
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Asp Val Leu Ile Asn Asn Ala Gly Ile Phe Gln Cys Pro Tyr Met Lys
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                                                    110
Thr Glu Asp Gly Phe Glu Met Gln Phe Gly Val Asn His Leu Gly His
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Phe Leu Leu Thr Asn Leu Leu Leu Gly Leu Leu Lys Ser Ser Ala Pro
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Ser Arg Ile Val Val Val Ser Ser Lys Leu Tyr Lys Tyr Gly Asp Ile
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Tyr Ser Arg Ser Lys Leu Ala Asn Ile Leu Phe Thr Arg Glu Leu Ala
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Arg Arg Leu Glu Gly Thr Asn Val Thr Val Asn Val Leu His Pro Gly
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Ile Val Arg Thr Asn Leu Gly Arg His Ile His Ile Pro Leu Leu Val
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Lys Pro Leu Phe Asn Leu Val Ser Trp Ala Phe Phe Lys Thr Pro Val
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Glu Gly Ala Gln Thr Ser Ile Tyr Leu Ala Ser Ser Pro Glu Val Glu
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Gly Val Ser Gly Arg Tyr Phe Gly Asp Cys Lys Glu Glu Glu Leu Leu
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Pro Lys Ala Met Asp Glu Ser Val Ala Arg Lys Leu Trp Asp Ile Ser
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					_	act Thr 55					-		-	_	•	192
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		_				cag G1n						_			_	288
						agc Ser										336
					_	cca Pro						_	-	-	_	384
Glu					Asp	gaa Glu 135				-					-	432
						gga Gly		-		-	_			_	_	480
						cgc Arg		-								528
tcc	tta	tcc	aat.	gga	aca	aat.	gat	act.	gac	cta	ttt	gat	tca	cat	gat	576

Ser	Leu	Ser	Asn 180	Gly	Thr	Ser	Asp	Ala 185	Asp	Leu	Phe	Asp	Ser 190	His	Asp	
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-	atc Ile 210	_			-	-	_	_	_			-				672
_	gta Val	-			_				_	-	_				-	720
_	tat Tyr	-	-			-		_	-				_		-	768
-	cag Gln	_	_		-	_	_									816
	tca Ser															864
	aat Asn 290															912
	gat Asp		•				-		-		-			_		960
	gtt Val				-	-				_						1008
	cca Pro				•			_		_			_	_		1056
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-	_				ctc Leu 390											1200
					gtg Val	-				_	_				-	1248
					agt Ser	-										1296
			-	_	cac His	_			-							1344
					tgc Cys			-		-					_	1392
	-			-	aca Thr 470		_			-		-	-		-	1440
					aag Lys	-										1488
-		_		_	agc Ser			-	-	-						1536
					gca Ala			-								1584
aga	caa	aga	gca	gaa	gcc	cga	gaa	agg	aag	gag	aag	gaa	att	cag	tgg	1632

Arg	G1n 530	Arg	Ala	Glu	Ala	Arg 535	Glu	Arg	Lys	Glu	Lys 540	Glu	Ile	Gln	Trp	
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Ser	Thr 50		Pro	Ser	G1n	Thr 55		Leu	Pro	Pro	Glu 60		Val	Gln	Leu	
Cys 65		Ser	Glu	G1n	Arg 70	Pro	Ser	Ser	Leu	Pro 75	Val	Gly	Pro	Val	Leu 80	
Ala	Thr	Leu	Gly	His 85	His	Gln	Thr	Pro	Thr 90	Pro	Asn	Ser	Thr	G1y 95	Ser	
Gly	His	Ser	Pro 100	Pro	Ser	Ser	Ser	Leu 105	Thr	Ser	Pro	Ser	His 110	Val	Asn	
Leu	Ser	Pro 115	Asn	Thr	Val	Pro	G1u 120	Phe	Ser	Tyr	Ser	Ser 125	Ser	Glu	Asp	
Glu	Phe 130	Tyr	Asp	Ala	Asp	Glu 135	Phe	His	Gln	Ser	Gly 140	Ser	Ser	Pro	Lys	
Arg 145	Leu	Пe	Asp	Ser	Ser 150	Gly	Ser	Ala	Ser	Val 155	Leu	Thr	His	Ser	Ser 160	
Ser	Gly	Asn	Ser	Leu 165	Lys	Arg	Pro	Asp	Thr 170	Thr	Glu	Ser	Leu	Asn 175	Ser	
Ser	Leu	Ser	Asn 180	Gly	Thr	Ser	Asp	Ala 185	Asp	Leu	Phe	Asp	Ser 190	His	Asp	
Asp	Arg	Asp 195	Asp	Asp	Ala	Glu	A1 a 200	Gly	Ser	Val	Glu	G1u 205	His	Lys	Ser	

Val	Ile 210	Met	His	Leu	Leu	Ser 215	Gln	Val	Arg	Leu	G1y 220	Met	Asp	Leu	Thr
Lys 225	Val	Val	Leu	Pro	Thr 230	Phe	Ile	Leu	Glu	Arg 235	Arg	Ser	Leu	Leu	G1u 240
Met	Tyr	Ala	Asp	Phe 245	Phe	Ala	His	Pro	Asp 250	Leu	Phe	۷a۱	Ser	Ile 255	Ser
Asp	Gln	Lys	Asp 260	Pro	Lys	Asp	Arg	Met 265	Val	Gln	Val	Val	Lys 270	Trp	Tyr
Leu	Ser	A1 a 275	Phe	His	Ala	Gly	Arg 280	Lys	Gly	Ser	Val	A1a 285	Lys	Lys	Pro
Tyr	Asn 290	Pro	Пe	Leu	Gly	G1u 295	Пe	Phe	Gln	Cys	His 300	Trp	Thr	Leu	Pro
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	•	435	Lys				440					445			•
	450		Ser		•	455			•		460				
Tyr 465		Lys	Tyr			Gly						Val	Asp		Lys 480
Lys	Leu	Pro	He	I le 485	Lys	Lys	Lys	Val	Arg 490	Lys	Leu	Glu	Asp	G1n 495	Asn
Glu	Tyr	Glu	Ser 500	Arg	Ser	Leu	Trp	Lys 505	Asp	Val	Thr	Phe	Asn 510	Leu	Lys
Пе	Arg	Asp 515	Пe	Asp	Ala	Ala	Thr 520	Glu	Ala	Lys	His	Arg 525	Leu	Glu	Glu
Arg	G1n 530	Arg	Ala	Glu	Ala	Arg 535	Glu	Arg	Lys	Glu	Lys 540	Glu	Ile	Gln	Trp
G1u 545	Thr	Arg	Leu	Phe	His 550	Glu	Asp	Gly	Glu	Cys 555	Trp	Val	Tyr	Asp	G1u 560

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					gct Ala											192
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				-	aag Lys	_							-			288
					ctg Leu											336
tac	acc	tct	gca	gtt	tcc	atg	gtc	aaa	cct	cac	atg	gtc	aag	gct	gtt	384

Tyr Thr Ser Ala Val Ser Met Val Lys Pro His Met Val Lys Ala Val

125

120

						ttc Phe 135								-		432
						tat Tyr									_	480
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Thr			Arg	Lys	Ala	Tyr 55		Glu	Arg	Arg	Ile 60		Gly	Tyr	Ser	
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	Val	Pro	Trp	Cys 85		Lys	Ser	Leu	Va1 90		Ser	Ser	Arg	Lys 95		

124 His Leu Lys Ala Gln Leu Glu Val Gly Phe Pro Pro Val Met Glu Arg 105 Tyr Thr Ser Ala Val Ser Met Val Lys Pro His Met Val Lys Ala Val 120 Cys Thr Asp Gly Lys Leu Phe Asn His Leu Glu Thr Ile Trp Arg Phe 135 140 Ser Pro Gly Ile Pro Ala Tyr Pro Arg Thr Cys Thr Val Asp Phe Ser 145 150 155 160 Ile Ser Phe Glu Phe Arg Ser Leu Leu His Ser Gln Leu Ala Thr Met 165 170 Phe Phe Asp Glu Val Val Lys Gln Asn Val Ala Ala Phe Glu Arg Arg 180 185 Ala Ala Thr Lys Phe Gly Pro Glu Thr Ala Ile Pro Arg Glu Leu Met 195 200 205 Phe His Glu Val His Gln Thr 210 215 <210> 85 <211> 615 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(615) <400> 85 atg ggg ttt ctg acc tcc tqc agc ctc ctc ttg cct cqq qct qcc caq 48 Met Gly Phe Leu Thr Ser Cys Ser Leu Leu Leu Pro Arg Ala Ala Gln 1 5 10 15 atc ttg gcg gct gag gct ggc tta cct tcg agc cgt tcc ttc atg gga 96 Ile Leu Ala Ala Glu Ala Gly Leu Pro Ser Ser Arg Ser Phe Met Gly 20 25 ttt gct gct ccc ttc acc aac aag cga aag gct tac tcg gag cgt aga 144 Phe Ala Ala Pro Phe Thr Asn Lys Arg Lys Ala Tyr Ser Glu Arg Arg 35 40 atc atg ggg tac tca atg cag gag atg tat gag gtg gtg tcc aac gtc 192

Ile Met Gly Tyr Ser Met Gln Glu Met Tyr Glu Val Val Ser Asn Val

cag gag tat cgt gag ttt gtg ccc tgg tgt aag aag tct ctg gtg gta

60

240

55

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	gtc Val	_	-	-				-	_		_	_				336
	gtc Val															384
	att Ile 130		-		-					-			-		-	432
	gtg Val	•		•				•		•		_	•			480
	ctg Leu			_			-			-		-		-	•	528
_	ttt Phe		-		-	-		-				-		_		576
	cgt Arg	_	_	_						-		-				615
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He	Met 50		Tyr	Ser	Met	Gln 55	Glu	Met	Tyr	Glu	Va1 60	Val	Ser	Asn	Val	
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-	gct Ala	-	-		-	_		_	-	_			-		_	96
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127

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						-		-	-	-				gac Asp		336
				-			-	_		-	-	-	_	gaa Glu		384
					_		_	-	-	-	_			cta Leu		432
				-	_	-	_	-						ttg Leu		480
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Leu	Asn 50	Ala	Ala	Leu	Asp	Leu 55	Leu	Gly	Gly	Glu	Asp 60	Gly	Leu	Cys	Gln	
Tyr 65	Ļys	Cys	Ser	Asp	Gly 70	Ser	Lys	Pro	Phe	Pro 75	Arg	Tyr	Gly	Tyr	Lys 80	
Pro	Ser	Pro	Pro	Asn 85	Gly	Cys	Gly	Ser	Pro 90	Leu	Phe	Gly	Val	His 95	Leu	
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Cys	Tyr	G1u 115	Thr	Cys	Gly	Lys	Ser 120	Lys	Asn	Asp	Cys	Asp 125	Glu	Glu	Phe	
Gln	Tyr 130	Cys	Leu	Ser	Lys	Ile 135	Cys	Arg	Asp	Val	Gln 140	Lys	Thr	Leu	Gly	
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							_	ggc Gly 25		-						96

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-	_			_							_	_		atg Met 95	-	288
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			-	-		_	-		_		-	_	-	cgg Arg	_	432
					_				-				-	atc Ile		480
							_	-						gtc Val 175		528
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He	Va1 50	Glu	Val	Phe	Gly	Thr 55	G1u	Val	Leu	Leu	G1u 60	Asn	Gly	Asp	Ile	
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His	Thr ·	G1u 195	Leu	Glu	Arg	Ser	Leu 200	Glu	Tyr	Leu	Pro	Leu 205	Arg	Phe	Gly	
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                                                          15
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Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
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                                 25
cag atc atg cac ctg ctg agc gtg ggc tcc atc ctg cag ctg cac gcc
                                                                      144
Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
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Lys Arg Ala Arg Leu Leu Tyr Glu Ser Arg Lys Arg Gly Met Leu Glu

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	-		-	_								aac Asn			-	336
	-					-	-	-			-	aaa Lys 125		-		384
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Ile	Pro 50		Pro	Pro	Trp	G1n 55		Arg	Thr	Asp	Glu 60	Ser	Пе	Glu	Thr	
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Phe	Glu	Lys	Pro	Arg 165												
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			ttg Leu				_		-						-	192
		_	gcc Ala	-	-				_	-	_			_	_	240
_		-	att Ile			_			-		-		_	_		288

				85					90					95		
_		-	-	_	-				_	_	ctg Leu					336
-		_									gaa Glu					384
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Arg	Phe	Tyr 35	Arg	Gly	Asp	Ser	Pro 40	Thr	Asp	Ser	Gln	Lys 45	Asp	Met	Ile	
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Thr 65		Arg	Ala	Arg	Leu 70		Tyr	Glu	Ser	Arg 75	Lys	Arg	Gly	Met	Leu 80	
	Asn	Cys	Пe	Leu 85	. •	Ser	Leu	Phe	Ala 90		Glu	His	Leu	G1n 95		
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Ser	Asn	Asp		Asp	Пe	Tyr	Tyr		Ala	Thr	Glu	Ala		Pro	Ala	

Pro		115 Ile	Phe	Glu	Asn	Glu	120 Val	Met	Ala	Leu		125 Arg	Asp	Phe	Ala	
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		-				ggc Glv	_	_		_						336

			100					105					110				
						_	gct Ala 120							_			384
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Ala	Val	Pro 35		Leu	Gly	Thr	Tyr 40		Ala	Ala	Val	Pro 45		Val	Leu		
Asp	Leu 50		Leu	Thr	Gln	Gly 55	Leu	Gly	Cys	Lys	A1a 60		Leu	Leu	Leu	-	
I1e 65		His	Leu	Leu	Pro 70		Tyr	Phe	Val	Asp 75		Ala	Пе	Tyr	Ser 80		
	He	Ser	Gly	G1 <i>y</i> 85		His	Pro	Tyr	Leu 90		Gly	Leu	Ala	Va1 95			
Gly	Gly	Ala	Tyr 100		Leu	Gly	Leu	Glu 105		Ala	Пе	Ile	Gly 110		Ile		
Leu	Leu	Cys 115		Leu	Val	Val	Ala 120		Asn	Пе	Tyr	Ser 125		Met	Leu		
Val	Ser 130		Thr	Asn	Ser	Val 135	Pro	Thr	Pro	Asn	G1n 140		Pro	Trp	Pro		
۸٦.		Dro.	Cln	۸na	The		Ara	۸cn	מנז	Sar		Acn	Lou	L vc	Son		

138

145 150 155 160 Ser Val Gly <210> 99 <211> 1464 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1464) <221> misc feature <222> (1)...(1464) <223> n = A,T,C or G<400> 99 atg tgg gga cct aac tcc tat gca tgg gtg ctc atg cag ttg gcc acc 48 Met Trp Gly Pro Asn Ser Tyr Ala Trp Val Leu Met Gln Leu Ala Thr 10 gcc cag gcg ggc atc att ctg gtg tct gtg aac cca gcc tac cag gct 96 Ala Gln Ala Gly Ile Ile Leu Val Ser Val Asn Pro Ala Tyr Gln Ala 20 25 30 atg gaa ctg gag tac gtc ctc aag aag gtg ggc tgc aag gcc ctt gtg 144 Met Glu Leu Glu Tyr Val Leu Lys Lys Val Gly Cys Lys Ala Leu Val 35 40 ttc ccc aag caa ttc aag acc cag caa tac tac aac gtc ctg aag cag 192 Phe Pro Lys Gln Phe Lys Thr Gln Gln Tyr Tyr Asn Val Leu Lys Gln 50 55 atc tgt cca gaa gtg gag aat gcc cag cca ggg gcc ttg aag agt cag 240 Ile Cys Pro Glu Val Glu Asn Ala Gln Pro Gly Ala Leu Lys Ser Gln 65 70 75 80 agg ctc cca gat ctg acc aca gtc atc tcg gtg gat gcc cct ttg ccg 288 Arg Leu Pro Asp Leu Thr Thr Val Ile Ser Val Asp Ala Pro Leu Pro 85 90 ggg acc ctg ctc ctg gat gaa gtg gtg gcg gct ggc agc aca cgg cag 336 Gly Thr Leu Leu Leu Asp Glu Val Val Ala Ala Gly Ser Thr Arg Gln

	100	105		110
		_	cag ttc ctg tcc Gln Phe Leu Ser 125	•
	Ile Gln Phe		aca aca ggc agc Thr Thr Gly Ser 140	
•		_	aac aac tcc aac Asn Asn Ser Asn 155	<del></del>
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	-	-	ggt tcc gtg gca Gly Ser Val Ala	
		-	atc ctg gcc tct Ile Leu Ala Ser 205	
	Lys Ala Leu		agc aga gag aga Ser Arg Glu Arg 220	
	Thr Pro Thr		gac att ctg aac Asp Ile Leu Asn 235	-
			tgt gga ggt gtc Cys Gly Gly Val 250	
			gcc atc atc aac Ala Ile Ile Asn	
			acc aca gag aac Thr Thr Glu Asn	

	275					280					285					
					gag G1u 295										9	12
			-		cac His	_	-				-		_			60
				_	ctg Leu		_				_	-		-	10	80
				_	ggc Gly						_	-			10	56
	_	-	-	-	aag Lys						-	-	-		11	04
					tgc Cys 375	_				-		-	-	-	11!	52
			-		aac Asn				_				_		120	00
		His	Pro	Lys	ntg Xaa	Gln	Glu	Val	Gln					Lys	124	48
					gag Glu										129	96
 -			-		gag G1u				_		-			_	134	14
					ccg Pro										139	92

141

450 455 460 ccc ctc acc att tca gga aag atc cag aaa ttc aaa ctt cga gag cag 1440 Pro Leu Thr Ile Ser Gly Lys Ile Gln Lys Phe Lys Leu Arg Glu Gln 465 470 475 atg gaa cga cat cta aat ctg tga 1464 Met Glu Arg His Leu Asn Leu \* 485 <210> 100 <211> 487 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(487) <223> Xaa = Any Amino Acid <400> 100 Met Trp Gly Pro Asn Ser Tyr Ala Trp Val Leu Met Gln Leu Ala Thr 10 Ala Gln Ala Gly Ile Ile Leu Val Ser Val Asn Pro Ala Tyr Gln Ala 25 Met Glu Leu Glu Tyr Val Leu Lys Lys Val Gly Cys Lys Ala Leu Val 40 45 Phe Pro Lys Gln Phe Lys Thr Gln Gln Tyr Tyr Asn Val Leu Lys Gln 55 60 Ile Cys Pro Glu Val Glu Asn Ala Gln Pro Gly Ala Leu Lys Ser Gln 70 75 Arg Leu Pro Asp Leu Thr Thr Val Ile Ser Val Asp Ala Pro Leu Pro 90 Gly Thr Leu Leu Leu Asp Glu Val Val Ala Ala Gly Ser Thr Arg Gln 105 110 His Leu Asp Gln Leu Gln Tyr Asn Gln Gln Phe Leu Ser Cys His Asp 120 Pro Ile Asn Ile Gln Phe Thr Ser Gly Thr Thr Gly Ser Pro Lys Gly 135 Ala Thr Leu Ser His Tyr Asn Ile Val Asn Asn Ser Asn Ile Leu Gly 150 155 Glu Arg Leu Lys Leu His Glu Lys Thr Pro Glu Gln Leu Arg Met Ile

170

Leu	Pro	Asn	Pro 180	Leu	Tyr	His	Cys	Leu 185	Gly	Ser	Val	Ala	Gly 190	Thr	Met
Met	Cys	Leu 195	Met	Tyr	Gly	Ala	Thr 200	Leu	Ile	Leu	Ala	Ser 205	Pro	Ile	Phe
Asn	Gly 210	Lys	Lys	Ala	Leu	G1u 215	Ala	Пe	Ser	Arg	G1u 220	Arg	Gly	Thr	Phe
Leu 225	Tyr	Gly	Thr	Pro	Thr 230	Met	Phe	Val	Asp	I1e 235	Leu	Asn	Gln	Pro	Asp 240
Phe	Ser	Ser	Tyr	Asp 245	ΙΊe	Ser	Thr	Met	Cys 250	Gly	Gly	Val	Ile	A1a 255	Gly
Ser	Pro	Ala	Pro 260	Pro	Glu	Leu	Ile	Arg 265	Ala	Ile	Ile	Asn	Lys 270	He	Asn
Met	Lys	Asp 275	Leu	Val	Val	Ala	Tyr 280	Gly	Thr	Thr	Glu	Asn 285	Ser	Pro	Val
	290				Pro	295	·				300	-			
Va1 305	Gly	Arg	Ile	Met	Pro 310	His	Thr	Glu	Ala	Arg 315	Ile	Met	Asn	Met	G1u 320
				325	Lys				330					335	Ī
Gly	Tyr	Cys	Va1 340	Met	Leu	Gly	Tyr	Trp 345	Gly	Glu	Pro	Gln	Lys 350	Thr	Glu
Glu	Ala	Va1 355	Asp	G1n	Asp	Lys	Trp 360	Tyr	Trp	Thr	Gly	Asp 365	Val	Ala	Thr
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Ile 385	Ile	Arg	Gly	Gly	G1u 390	Asn	Ile	Tyr	Pro	Ala 395	Glu	Leu	Glu	Asp	Phe 400
Phe	His	Thr	His	Pro 405	Lys	Xaa	Gln	Glu	Val 410	Gln	Val	Val	Gly	Val 415	Lys
Asp	Asp	Arg	Met 420	Gly	Glu	Glu	Пe	Cys 425	Ala	Cys	Пe	Arg	Leu 430	Lys	Asp
	Glu			Thr	Val	Glu				Ala		Cys 445	Lys	Gly	Lys
Ile	Ser 450	His	Phe	Lys	Пe	Pro 455	Lys	Tyr	Ile	Val	Phe 460	Val	Thr	Asn	Tyr
Pro 465	Leu	Thr	Ile	Ser.	Gly 470	Lys	Ile	Gln	Lys	Phe 475	Lys	Leu	Arg	Glu	Gln 480
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143

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			atg ggg gac at Met Gly Asp Me		96									
		• •	atc ctg att gg Ile Leu Ile Gl 4	y Leu Gly Leu	144									
	•		gat tac gga tc Asp Tyr Gly Se 60		192									
			gta ggc ttg ct Val Gly Leu Le 75		240									
			ctg aac aag tg Leu Asn Lys Tr 90		288									
			ctg tat ggg tg Leu Tyr Gly Cy		336									
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<211> 115

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<213> Homo sapiens

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Asn	Ser	Ile 35	Gly	Ser	Asn	Val	Phe 40	Asp	Ile	Leu	Ile	Gly 45	Leu	Gly	Leu		
Pro	Trp 50	Ala	Leu	Gln	Thr	Leu 55	Ala	Val	Asp	Tyr	Gly 60	Ser	Tyr	Ile	Arg		
Leu 65	Asn	Ser	Arg	Gly	Leu 70	Ile	Tyr	Ser	Val	G1y 75	Leu	Leu	Leu	Ala	Ser 80		
Val	Phe	Val	Thr	Va1 85	Phe	Gly	Val	His	Leu 90	Asn	Lys	Trp	Gln	Leu 95	Asp		
Lys	Lys	Leu	Gly 100	Cys	Gly	Cys	Leu	Leu 105	Leu	Tyr	Gly	Cys	Ser 110	Cys	Ala		
Ser	Pro	Ser 115															
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			1239														
				DNA Homo sapiens													
	~	213>	ПОНІС	) 2at	rens	•											
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		221> 222>	CDS (1)(1239)													-	
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		100>												,		40	
				gtg Val 5												48	
cgg	ggc	ggc	agc	cga	ttc	ctq	qcc	acc	tcc	ata	gca	agc	agt	gat	gat	96	
				Arg													
gac	agc	ctc	ttc	atc	tať	gac	tgc	agt	gct	gca	gaa	aag	aag	tca	caa	144	
Asp	Ser	Leu 35	Phe	Ilė	Tyr	Asp	Cys 40	Ser	Ala	Ala	Glu	Lys 45	Lys	Ser	Gln		
asp	aat	aaa	gaa	gag	gac	qca	CCC	tta	gac	caq	ggg	agc	gat	qca	att	192	
				Glu												204	

-						_			_			_	tta Leu		•		240
_	-	-	-	_				_					caa G1n	_	-		288
-	-				-			-		_	-		ttc Phe 110		-	•	336
_			-	-	-		-	-	_				gtc Val				384
													ctg Leu				432
-		-	_		-		_		_				cgc Arg				480
		-	-				-		-	-	_		gcc Ala				528
		-					-	_					ttt Phe 190		-		576
													tcc Ser				624
													cgc Arg			٠.	672
		-			-	-	_	_		-			ccc Pro				720

	cag Gln															768
	gtg Val															816
-	gac Asp		_	-	_	_										864
_	cac His 290				-		_		-	-				-		912
	ctc Leu	-	-	-	-	_	_		-							960
	gac Asp	-		_		-			_						_	1008
	ggt Gly	_		_					-							1056
_	gac Asp	-	_		_	-			-	-	-		-			1104
	tcc Ser 370		-	-	_			-	_							1152
	aag Lys															1200
-	aag Lys	_	-	_				_				tga *				1239

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PCT/US00/29052

Gln His Gln Val Trp Asp Val Ala Phe Glu Glu Thr Gln Gly Leu Trp 290 295 300 Val Leu Gln Asp Cys Gln Glu Ala Pro Leu Val Leu Tyr Arg Pro Val 305 310 315 Gly Asp Gln Trp Gln Ser Val Pro Glu Ser Thr Val Leu Lys Lys Val 325 330 Ser Gly Val Leu Arg Gly Asn Trp Ala Met Leu Glu Gly Ser Ala Gly 345 350 Ala Asp Ala Ser Phe Ser Ser Leu Tyr Lys Ala Thr Phe Asp Asn Val 360 365 Thr Ser Tyr Leu Lys Lys Glu Glu Arg Leu Gln Gln Gln Leu Glu 380 375 Lys Lys Gln Arg Arg Arg Ser Pro Pro Pro Gly Pro Asp Gly His Ala 395 385 390 400 Lys Lys Met Arg Pro Gly Glu Ala Thr Leu Ser Cys 410 405 <210> 105 <211> 645 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(645) <400> 105 atg agt gat ttg gaa gat gat gag aca ccc cag ctt tct gcc cat gcc 48 Met Ser Asp Leu Glu Asp Asp Glu Thr Pro Gln Leu Ser Ala His Ala 1 5 10 15 tta gca gct ctc cag gaa ttt tat gct gag caa aag caa caa att gag 96 Leu Ala Ala Leu Gln Glu Phe Tyr Ala Glu Gln Lys Gln Gln Ile Glu 20 25 30 144 cca ggc gag gat gat aaa tat aac att gga ata ata gaa gag aat tgg Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp caa ctg agc cag ttt tgg tat agt cag gaa act gct ctg cag ctg gca 192 Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala 50 55 60 240 cag gag gca att gca gct gta gga gaa ggt ggc aga atc gca tgt gtg

Gln 65	Glu	Ala	Ile	Ala	A1a 70	Val	Gly	Glu	Gly	Gly 75	Arg	Ile	Ala	Cys	Val 80	
						cag Gln										288
						gaa G1u									gga <sup>.</sup> Gly	336
						gat Asp										384
						ttt Phe 135										432
						aga Arg										480
						ctg Leu										528
_	_	-				gtg Val	-	-	-	_		-				576
			-	-		gag Glu										624
	ctg Leu 210					tga *										645

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Leu Ala Ala Leu Gln Glu Phe Tyr Ala Glu Gln Lys Gln Gln Ile Glu
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Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp
Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
                        55
                                             60
Gln Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
                    70
                                        75
Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
                                    90
                85
Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
                                105
Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
                        135
Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
145
                    150
                                        155
Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
                165
                                    170
Ala Ala Glu Leu Leu Gly Val Lys Met Cys Thr Phe Val Pro Arg His
                                185
Thr Arg Asn Leu Ala Asn Glu Phe Arg Cys Tyr Val Asn Tyr Asp Ser
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                            200
                                                 205
Gly Leu Asp Cys Gly Ile
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Met Lys Ser Ser Thr Leu Leu Thr Ile Leu Val Leu Gln Ala Leu Leu
 1
                                     10
                                                          15
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151

	tct Ser												_	_	-	96
	tgc Cys			_		_		_					-	-	-	144
	ctc Leu 50													-		192
	gac Asp	_		-		_		-	_	_	_				_	240
	tgc Cys						tag *	,								264
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Val	Ser	Thr	Ala 20	Val	Pro	Lys	Gly	Pro 25	Ala	Gly	Pro	Lys	Lys 30	Gln	Cys	
Trp	Cys	Gly 35	Glu	Cys	Thr	Ser	Trp 40	Ser	Gly	Val	Trp	Thr 45	Cys	Asp	Asp	
Leu	Leu 50	Thr	Lys	Cys	Ala	Ala 55	Thr	Cys	Lys	Asn	Cys 60	Val	Pro	Val	Ser	
Thr 65	Asp	Lys	Gly <sub>.</sub>	Ala	Thr 70	Lys	Tyr	Arg	Cys	Arg 75	Asp	Phe	Leu	Pro	Glu 80	
	Cys	Gly	Cys	Lys 85		His				, <u>J</u>						
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														gaa Glu	96
	-										-		-	gcc Ala	144
					-	-		_	-			-	-	atg Met	192
					-		_							acg Thr	240
_	-				_		-	-	_		-		-	tcg Ser 95	288
		-		-			_		-	_	_			caa G1n	336
					gaa Glu								tag *		378

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<213> Homo sapiens

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Val	Glu	Ser	Ile 20	Cys	Ser	Asn	Asn	Phe 25	Asp	Ser	Phe	Leu	His 30	Glu	Thr		
His	Glu	Asn 35	Lys	Tyr	G1y	Lys	G1y 40	Пe	Tyr	Phe	Ala	Lys 45	Asp	Ala	Ile		
Tyr	Ser 50	His	Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60	Val	Val	Met	Phe		
65					70					75				Thr	80		
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	Val	Asp	Thr	Arg	Ser 95	Asn		
Pro	Ser	Val	Phe 100	Val	He	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110	Gln	Tyr		
Val	Ile	G1u 115	Tyr	Thr	Glu	Asp	Lys 120	Ala	Cys	Val	Пe	Ser 125					
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	<2	220> 221> 222>	CDS (1).	(1	1965)	)											
>+ <i>a</i>		×00>			++-			+	+		+	~~~	+			A (	^
							-							ccg Pro 15	-	48	3
								_					-	gcc Ala		96	5
														aat Asn		144	1
														act Thr	-	192	2

	_	 _	_		_	-	gaa Glu	_			-	_	-		240
-		 _					ttt Phe				-			• •	288
							att Ile 105								336
							aaa Lys								384
							aca Thr								432
						-	caa Gln		_			-			480
		_	-	_	-	-	tca Ser	-			-	-		_	528
		_			_	_	tat Tyr 185	_			-		_		576
		-	-		_	-	caa Gln	-							624
							ttg Leu			-				-	672
							ctt Leu	_				_	-	_	720

						aac Asn			_	-					-	768
				-	-	tca Ser		-		_	-			-	-	816
		-	_	-		gaa G1u	-			_	-	-	_	-		864
					-	tat Tyr 295							_	-		912
-	_			_		gag Glu		_		-	,		_	-	_	960 <sup>°</sup>
-	-	-			_	gct Ala	_		•		-			_		1008
			-	-		tct Ser				-					-	1056
-	-	_	_	-	_	tgt Cys	_	-					-			1104
						tat Tyr 375										1152
					-	tat Tyr		_			-	-			_	1200
						gaa Glu	-			-						1248

		-	_			-						-		aaa Lys	_	1296
		_							-	-			Ser	ccc Pro		1344
				- •	-				-					gtg Val	-	1392
	_	-	-	_		_	_			_	_		-	acc Thr	_	1440
			-	-			-							ctt Leu 495	-	1488
					_	-		-	_	-				aat Asn		1536
														ata Ile		1584
_		-	_		-									aag Lys		1632
														tca Ser		1680
					_									act Thr 575		1728
														caa G1n		1776

157

				-	aac Asn	_					-					1824
-		-	-		ttg Leu	-	-	-		-	-		-		-	1872
-	_				acc Thr 630	_	_		-		-			_		1920
			-	-	gag Glu						_	-		tga *		1965
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1	Ala	Ala	Ala	5	Leu Gln				10					15		
1 Val	Ala Ala	Ala Glu	Ala Leu 20	5 Cys		Asn	Thr	Pro 25	10 Glu	Thr ·	Phe	Leu	G1u 30	15 Ala	Ser	
1 Val Lys	Ala Ala Leu	Ala Glu Leu 35	Ala Leu 20 Leu	5 Cys Thr	Gln	Asn Ala	Thr Asp 40	Pro 25 Asn	10 Glu Ile	Thr Leu	Phe Arg	Leu Asn 45	Glu 30 Pro	15 Ala Asn	Ser Asp	
1 Val Lys Glu	Ala Ala Leu Lys 50	Ala Glu Leu 35 Tyr	Ala Leu 20 Leu Arg	5 Cys Thr Ser	Gln Tyr	Asn Ala Arg 55	Thr Asp 40 Ile	Pro 25 Asn Gly	10 Glu Ile Asn	Thr Leu Thr	Phe Arg Ala 60	Leu Asn 45 Phe	Glu 30 Pro Ser	15 Ala Asn Thr	Ser Asp Arg	
1 Val Lys Glu Leu 65	Ala Ala Leu Lys 50 Leu	Ala Glu Leu 35 Tyr Pro	Ala Leu 20 Leu Arg Val	5 Cys Thr Ser Arg	Gln Tyr Ile Gly	Asn Ala Arg 55 Ala	Thr Asp 40 Ile Val	Pro 25 Asn Gly Glu	10 Glu Ile Asn Cys	Thr Leu Thr Leu 75	Phe Arg Ala 60 Phe	Leu Asn 45 Phe Glu	Glu 30 Pro Ser Met	15 Ala Asn Thr Gly	Ser Asp Arg Phe	
1 Val Lys Glu Leu 65 Glu	Ala Ala Leu Lys 50 Leu Glu	Ala Glu Leu 35 Tyr Pro Gly	Ala Leu 20 Leu Arg Val	5 Cys Thr Ser Arg Thr 85	Gln Tyr Ile Gly 70	Asn Ala Arg 55 Ala Leu	Thr Asp 40 Ile Val	Pro 25 Asn Gly Glu Phe	10 Glu Ile Asn Cys Pro 90	Thr Leu Thr Leu 75 Lys	Phe Arg Ala 60 Phe Lys	Leu Asn 45 Phe Glu Ala	Glu 30 Pro Ser Met	15 Ala Asn Thr Gly Val 95	Ser Asp Arg Phe 80 Glu	
1 Val Lys Glu Leu 65 Glu	Ala Ala Leu Lys 50 Leu Glu Leu	Ala Glu Leu 35 Tyr Pro Gly	Ala Leu 20 Leu Arg Val Glu Lys 100	5 Cys Thr Ser Arg Thr 85 Ile	Gln Tyr Ile Gly 70 His	Asn Ala Arg 55 Ala Leu Asp	Thr Asp 40 Ile Val Ile Leu	Pro 25 Asn Gly Glu Phe Ile 105	10 Glu Ile Asn Cys Pro 90 Ala	Thr Leu Thr Leu 75 Lys	Phe Arg Ala 60 Phe Lys Glu	Leu Asn 45 Phe Glu Ala Arg	Glu 30 Pro Ser Met Ser Ser 110	Asn Thr Gly Val 95 Ser	Ser Asp Arg Phe 80 Glu Arg	
1 Val Lys Glu Leu 65 Glu Gln Leu	Ala Leu Lys 50 Leu Glu Leu Asp	Ala Glu Leu 35 Tyr Pro Gly Gln Gly 115	Ala Leu 20 Leu Arg Val Glu Lys 100 Ser	5 Cys Thr Ser Arg Thr 85 Ile Asn	Gln Tyr Ile Gly 70 His	Asn Ala Arg 55 Ala Leu Asp	Thr Asp 40 Ile Val Ile Leu His 120	Pro 25 Asn Gly Glu Phe Ile 105 Lys	10 Glu Ile Asn Cys Pro 90 · Ala	Thr Leu Thr Leu 75 Lys Ile Lys	Phe Arg Ala 60 Phe Lys Glu Ser	Leu Asn 45 Phe Glu Ala Arg Ser 125	Glu 30 Pro Ser Met Ser 110 Gln	Asn Thr Gly Val 95 Ser Gln	Ser Asp Arg Phe 80 Glu Arg Pro	
1 Val Lys Glu Leu 65 Glu Gln Leu Ala	Ala Leu Lys 50 Leu Glu Leu Asp Ala 130	Ala Glu Leu 35 Tyr Pro Gly Gln Gly 115 Ser	Ala Leu 20 Leu Arg Val Glu Lys 100 Ser Thr	5 Cys Thr Ser Arg Thr 85 Ile Asn Gln	Gln Tyr Ile Gly 70 His Arg	Asn Ala Arg 55 Ala Leu Asp Ser Pro 135	Thr Asp 40 Ile Val Ile Leu His 120 Thr	Pro 25 Asn Gly Glu Phe Ile 105 Lys Thr	10 Glu Ile Asn Cys Pro 90 Ala Val	Thr Leu Thr Leu 75 Lys Ile Lys Ser	Phe Arg Ala 60 Phe Lys Glu Ser Ser 140	Leu Asn 45 Phe Glu Ala Arg Ser 125 Asn	Glu 30 Pro Ser Met Ser 110 Gln Pro	Asn Thr Gly Val 95 Ser Gln Ser	Ser Asp Arg Phe 80 Glu Arg Pro	

Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	Ile	Leu	Glu	Val	Leu 175	Gln
Ser	Asn	Ile	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu
Lys	Ala	Leu 195	Ala	Cys	Ile	Pro	Val 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Ile	Asn	Пe	Ser
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys	Glu	G1u 240
	Phe			245					250		_		-	255	
	Arg		260	·				265				·	270		
·	Gly	275					280				·	285	-		
	Asn 290	_			_	295					300				
305		-			310		·			315				-	320
	Ala			325					330	·				335	
	Trp		340		_			345				·	350		_
	Ala	355		·			360					365			•
	G1y 370					375					380		•		
385	Asp				390					395					400
	Arg			405	_				410	-				415	
Leu	Asn	Lys	G1n 420	Arg	Gln	Leu	Phe	Leu 425	Ser	Glu	Asn	Arg	Arg 430	Lys	Glu
	Leu	435					440					445			
Thr	Pro 450	435 Lys	Pro	Gly	Glu	Leu 455	440 Gly	Gly	Arg	Ile	Ser 460	445 Gly	Ser	Val	Ala
Thr Trp 465	Pro 450 Arg	435 Lys Val	Pro Ala	Gly Arg	Glu Gly 470	Leu 455 Glu	440 Gly Met	Gly Gly	Arg Leu	Ile Gln 475	Ser 460 Arg	445 Gly Lys	Ser Glu	Val Thr	Ala Leu 480
Thr Trp 465 Phe	Pro 450	435 Lys Val Pro	Pro Ala Cys	Gly Arg Glu 485	Glu Gly 470 Asn	Leu 455 Glu Glu	440 Gly Met Lys	Gly Gly Ile	Arg Leu Ser 490	Ile Gln 475 Lys	Ser 460 Arg Gln	445 Gly Lys Leu	Ser Glu Ḥis	Val Thr Leu 495	Ala Leu 480 Cys

	Ile	Ser 515	Gly	Trp	Glu	Asn	Gly 520	Val	Trp	Lys	Met	G1u 525	Ser	Ile	Phe	
Arg	Lys 530		Glu	Thr	Asp	Trp 535	His	Met	Val	Tyr	Leu 540	Ala	Arg	Lys	Glu	
G1y 545	Ser	Ser	Phe	Ala	Tyr 550	Ile	Ser	Trp	Lys	Phe 555	Glu	Cys	Gly	Ser	Val 560	
Gly	Leu	Lys	Val	Asp 565	Ser	Ile	Ser	Пe	Arg 570	Thr	Ser	Ser	Gln	Thr 57.5	Phe	•
	Thr	•	580			•		585			·		590			
	Leu	595		•			600			-		605			•	
	Thr 610					615					620		·	_	·	
625		·			630					635				Asp	His 640	
Glu	Glu	Asn	Cys	Leu 645	Glu	He	He	He	Lys 650	Phe	Ser	Asp	Leu		÷	
		210> 211> 212> 213>	585 DNA	o sap	oiens	5										
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	tct Ser	100> gca	113 ttg	tgg	ctg											48
Met 1 tct	tct	100> gca Ala	113 ttg Leu	tgg Trp 5	ctg Leu tgg	Leu gga	Leu tgc	Gly tat	Leu 10 gga	Leu aac	Ala atc	Leu caa	Met agc	Asp 15 ctg	Leu	48 96
Met 1 tct Ser	tct Ser gaa	100> gca Ala agc Ser	113 ttg Leu agc Ser 20 gca	tgg Trp 5 aac Asn	ctg Leu tgg Trp	gga Gly	tgc Cys	tat Tyr 25 gga	Leu 10 gga Gly aga	Leu aac Asn	Ala atc Ile	Leu caa Gln ggc	Met agc Ser 30 ctg	Asp 15 ctg Leu aac	Leu gac Asp	

160

	_					atg Met							_		_	240
						gct Ala		-	-			_				288
_			_	-		atg Met		-			-	_		•	•	336
						aca Thr								-		384
_			-	_	_	act Thr 135		-			-		_		~ ~	432
						gac Asp	_		_	_				_	_	480
	-			-		tat Tyr	-	-	-	-	-	-	_	_	-	528
_		_		-	_	ctt Leu	_	-	_	_			-	_		576
ggc Gly	ttc Phe	taa *														585

<210> 114

<211> 194

<212> PRT

<213> Homo sapiens

<400> 114

161

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Met Ser Ala Leu Trp Leu Leu Leu Gly Leu Leu Ala Leu Met Asp Leu
Ser Glu Ser Ser Asn Trp Gly Cys Tyr Gly Asn Ile Gln Ser Leu Asp
Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu Asn Tyr
                            40
Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
                        55
Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
                                        75
                    70
Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser Pro Gly
                                 - 90
Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
                                105
Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
                            120
Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
                        135
Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
                    150
                                        155
Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
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Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys Arg His
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Gly Phe
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					ctc Leu									-	_	96
_			_		cgc Arg			_			-	-	_			144
			_	-	ccc Pro	_					_	_				192
-			_	-	agc Ser 70	-	_	-		-					-	240
					ttc Phe									_		288
_	-	-	_	-	gct Ala		_				-	-	_			336
					gag Glu										-	384
					agc Ser									-	-	432
					acc Thr 150	-									_	480
					tct Ser			-	-							528
					gct Ala			-	-							576

-				-				-		-	gtc Val				-	624
			-		-		-			-	cgc Arg 220		-			672
-	-	-			_					-	gcg Ala	-		_		720
				_	-				-		ctc Leu	_			•	768
					-		_				acc Thr					816
-	_	-	-	-		_				-	gtc Val	_	-		•	864
											gtc Val 300					912
	tgg Trp	-	-	-	_	tga *										933

<210> 116

<211> 310

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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Glu	Ala	Val	G1n 20	Ala	Leu	Arg	Glu	Arg 25	Leu	Gly	Val	Gly	Gly 30	Arg	Thr
۷a٦ؚ	Gly	A1a 35	Leu	Pro	Arg	Gly	Pro 40	Arg	Gln	Asn	Ser	Arg 45	Leu	Gly	Leu
Pro	Leu 50	Leu	Leu	Met	Pro	Glu 55	Glu	Ala	Arg	Leu	Leu 60	Ala	Glu	Ile	Gly
Ala 65	Val	Thr	Leu	Val	Ser 70	Ala	Pro	Arg	Pro	Asp 75	Ser	Arg	His	His	Ser 80
Leu	Ala	Leu	Thr	Ser 85	Phe	Lys	Arg	Xaa	G1n 90	Glu	Glu	Ser	Phe	G1n 95	Glu
			100					105				_	G1n 110		
		115					120					125	Lys		
	130					135					140		Ser		
Ala 145	Lys	Glu	Asp	G1u	Thr 150	Ser	Asp	Gly	Gln	Ala 155	Ser	Gly	Glu	G1n	Glu 160
				165					170			•	Gly	175	
			180					185					Ala 190	_	
Arg	Pro	Val 195	Lys	Ala	Arg	Pro	Leu 200	Asp	Trp	Arg	Val	G1n 205	Ser	Lys	Asp
,	210					215					220		Ser		•
225					230	-				235			Gly	-	240
		-		245		-			250			_	Phe	255	
			260					265					Pro 270		
Asp	Leu	Val 275	Ala	Ala	Gly	Arg	Leu 280	Gly	Thr	Ser	Val	Arg 285	Lys	Thr	Leu
Leu	Leu 290	Cys	Ser	Pro	Gln	Pro 295	Asp	Gly	Lys	Val	Val 300	Tyr	Thr	Ser	Leu
G1n 305	Trp	Ala	Ser	Leu	G1n 310										

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	gca		ttc		ggc Gly							48
					tca Ser							96
					cca Pro							144
_	•	•			act Thr	_		-			-	 192
					999 Gly 70							240
		_		-	aat Asn		_	-				288
					gtt Val							336
					aga Arg							384
					tac Tyr							432

166

			tca Ser		_								-	-	_	4	180
			gag Glu					-				_	-			5	528
-		_	ctc Leu 180				-						_			5	576
			ttc Phe							-		-	_	_	_	6	524
			ctc Leu	_				_	-		_				-	6	572
			agc Ser											_		7	20
			atg Met	_	-					-					-	7	68
			tca Ser 260		-							_	_			8	16
	gag Glu	-	tga *													8	28
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Met Ala Asn Phe Lys Gly His Ala Leu Pro Gly Ser Phe Phe Leu Ile

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Ile Gly Leu Cys Trp Ser Val Lys Tyr Pro Leu Lys Tyr Phe Ser His
Thr Arg Lys Asn Ser Pro Leu His Tyr Tyr Gln Arg Leu Glu Ile Val
Glu Ala Ala Ile Arg Thr Leu Phe Ser Val Thr Gly Ile Leu Ala Glu
                        55
Gln Phe Val Pro Asp Gly Pro His Leu His Leu Tyr His Glu Asn His
Trp Ile Lys Leu Met Asn Trp Gln His Ser Thr Met Tyr Leu Phe Phe
                                    90
Ala Val Ser Gly Ile Val Asp Met Leu Thr Tyr Leu Val Ser His Val
                                105
Pro Leu Gly Val Asp Arg Leu Val Met Ala Val Ala Val Phe Met Glu
                            120
Gly Phe Leu Phe Tyr Tyr His Val His Asn Arg Pro Pro Leu Asp Gln
                        135
                                            140
His Ile His Ser Leu Leu Leu Tyr Ala Leu Phe Gly Gly Cys Val Ser
145
                    150
Ile Ser Leu Glu Val Ile Phe Arg Asp His Ile Val Leu Glu Leu Phe
                                    170
Arg Thr Ser Leu Ile Ile Leu Gln Gly Thr Trp Phe Trp Gln Ile Gly
                                185
Phe Val Leu Phe Pro Pro Phe Gly Thr Pro Glu Trp Asp Gln Lys Asp
                         - 200
Asp Ala Asn Leu Met Phe Ile Thr Met Cys Phe Cys Trp His Tyr Leu
                                            220
                        215
Ala Ala Leu Ser Ile Val Ala Val Asn Tyr Ser Leu Val Tyr Cys Leu
                   230
                                        235
Leu Thr Arg Met Lys Arg His Gly Arg Gly Glu Ile Ile Gly Ile Gln
                245
                                    250
Lys Leu Asn Ser Asp Asp Thr Tyr Gln Thr Ala Leu Leu Ser Gly Ser
            260
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Asp Glu Glu
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     <220>
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     <222> (1)...(867)
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_										_	-	-		ccc Pro	_	96
			_		-		_			-	-		_	ggc Gly		144
			_	_		-			_			-		ggc Gly	-	192
														tac Tyr		240
							_	-		-		-	_	gta Val 95	-	288
													-	att Ile	-	336
														gtt Val		384
														gtc Val		432
														ata Ile		480
							-	-						tgg Trp		528

169

				165				170				175		
	aca Thr				_			•						576
	ttg Leu						 -	-						624
	tat Tyr 210		-		_	-	 -					_	•	672
-	ccg Pro			_			 _			_				720
	tac Tyr		_			-							-	768
-	tca Ser				_						_		_	816
	aga Arg	-	_				 	-	-	_	_	_	-	864
taa *														867

<210> 120

<211> 288

<212> PRT

<213> Homo sapiens

<400> 120

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<400> 121

<222> (1)...(177)

171

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1				5					10				15		
				-	aac Asn								-		96
					gtg Val										. 144
		-	-		cag Gln		-	-						_	192
					ttg Leu 70										240
	_				ggt Gly	_		-		_	-				288
	_		_		agc Ser	_		-							336
			-		ctg Leu										384
Leu	Ala	Lys	Trp	Tyr	gag Glu	Lys	Phe	Phe	Gly	Arg	Leu	Ser			432
_	_	-			gct Ala 150	-	_	-	_						480
					gtc Val										528
		-	-	_	cag G1n									_	576

	180	185	190
	Phe Arg Ala Arg Se	ca gaa cct gag gac cca er Glu Pro Glu Asp Pro 205	Val Thr Glu
		at gct ggg agc ggg ctg sp Ala Gly Ser Gly Leu 220	
		ng gtc agc agc acg agc eu Val Ser Ser Thr Ser 235	
		ng gca gct tta gaa aag Bu Ala Ala Leu Glu Lys 250	<del>-</del>
*		et oot tot oto gto tgt eu Pro Ser Leu Val Cys 265	
	Pro Leu Arg Glu Ty	at tat agc cgc ctc atc or Tyr Ser Arg Leu Ile 30 285	His Gln Lys .
	•	gc acc ccc tgg ctg gag ys Thr Pro Trp Leu Glu 300	
		ng gac ctg ggt gtc tgt a Asp Leu Gly Val Cys 315	
		cc atg aag gtg gtg gac o Met Lys Val Val Asp 330	
		g aac ttc aag tgt tta 11 Asn Phe Lys Cys Leu 345	
		g gtc ttt gag gac tca u Val Phe Glu Asp Ser	

174

355 360 365 gca gct cag ctg cag atg ctt ttc tca aac ttt cct gat ctg cgg gca 1152 Ala Ala Gln Leu Gln Met Leu Phe Ser Asn Phe Pro Asp Leu Arg Ala 370 375 380 1158 agc taa Ser \* 385 <210> 124 <211> 385 <212> PRT <213> Homo sapiens <400> 124 Met Gln Tyr His Ala Leu Ser Leu Ala Met His Gly Phe Ser Val Thr Leu Leu Gly Phe Cys Asn Ser Lys Pro His Asp Glu Leu Leu Gln Asn Asn Arg Ile Gln Ile Val Gly Leu Thr Glu Leu Gln Ser Leu Ala Val Gly Pro Arg Val Phe Gln Tyr Gly Val Lys Val Val Leu Gln Ala Met 55 Tyr Leu Leu Trp Lys Leu Met Trp Arg Glu Pro Gly Ala Tyr Ile Phe Leu Gln Asn Pro Pro Gly Leu Pro Ser Ile Ala Val Cys Trp Phe Val 90 Gly Cys Leu Cys Gly Ser Lys Leu Val Ile Asp Trp His Asn Tyr Gly 105 Tyr Ser Ile Met Gly Leu Val His Gly Pro Asn His Pro Leu Val Leu 120 Leu Ala Lys Trp Tyr Glu Lys Phe Phe Gly Arg Leu Ser His Leu Asn 135 140 Leu Cys Val Thr Asn Ala Met Arg Glu Asp Leu Ala Asp Asn Trp His 150 155 Ile Arg Ala Val Thr Val Tyr Asp Lys Pro Ala Ser Phe Phe Lys Glu 165 170 Thr Pro Leu Asp Leu Gln His Arg Leu Phe Met Lys Leu Gly Ser Met 185 190 His Ser Pro Phe Arg Ala Arg Ser Glu Pro Glu Asp Pro Val Thr Glu 200 Arg Ser Ala Phe Thr Glu Arg Asp Ala Gly Ser Gly Leu Val Thr Arg

	210					215					220					
Leu 225	Arg	Glu	Arg	Pro	Ala 230	Leu	Leu	Val	Ser	Ser 235	Thr	Ser	Trp	Thr	G1u 240	
Asp	Glu	Asp	Phe	Ser 245	Ile	Leu	Leu	Ala	A1a 250	Leu	Glu	Lys	Phe	G1u 255	Gln	
Leu	Thr	Leu	Asp 260	Gly	His	Asn	Leu	Pro 265		Leu	Val	Cys	Val 270	Пe	Thr	
Gly	Lys	Gly 275	Pro	Leu	Arg	Glu	Tyr 280	Tyr	Ser	Arg		Ile 285	His	Gln	Lys	
His	Phe 290	Gln	His	He	Gln	Val 295	Cys	Thr	Pro	Trp	Leu 300	Glu	Ala	Glu	Asp	
Tyr 305	Pro	Leu	Leu	Leu	Gly 310	Ser	Ala	Asp	Leu	Gly 315	Val	Cys	Leu	His	Thr 320	
Ser	Ser	Ser	Gly	Leu 325	Asp	Leu	Pro	.Met	Lys 330	Val	Val	Asp	Met	Phe 335	Gly	
Cys	Cys	Leu	Pro 340	Val	Cys	Ala	Val	Asn 345	Phe	Lys	Cys	Leu	His 350	G1u	Leu	
Val	Lys	His 355	Glu	Glu	Asn	Gly	Leu 360	Val		G1u	Asp	Ser 365	Glu	Glu	Leu	
Ala	A1a 370	Gln	Leu	Gln	Met	Leu 375	Phe	Ser			Pro 380	Asp	Leu	Arg	Ala	
Ser 385		•														
		210>								•						
		211> 212>		2												
				sap	oiens	5										
		220> 221>	cne													
				(1	1002	)										
				_	ture											
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	gcg Ala															48
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	ggc Gly								_					-		96

			30					25					20			
144			_	-				_	_	gtc Val		_				_
192	_	_		-		-			-	atc Ile 55		-		-	-	
240			-			-		-		ccc Pro		-		_	-	
288	•	_	-						-	tct Ser						
336			-		_		-			cct Pro	-				_	-
384			-	-	-	-				gat Asp		-		_		-
432			-					_	-	gtt Val 135	-	-		-		
480	-									ctg Leu	_			-		
528	-	-	-							ctc Leu	_	_				
576			_							gtc Val			_			
624	-								-	aag Lvs						

		195					200					205					
-				_	ctg Leu	-		_								672	
-	-		-		aag Lys 230				_							720	J
_		_	_		cag Gln											768	;
-				-	atc Ile	_			-							816	)
	-	-	_	_	atg Met		•			_	•		_	•	•	864	
	-			_	.gcc Ala	-	-	_								912	
		-		_	tca Ser 310	_		_								960 -	<b></b>
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Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45	Gln	His	His
Arg	Thr 50	Val	His	Gln	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	Val
Tyr 65	Cys	Ser	Thr	Val	Va1 70	Pro	Ser	Asp	Asp	Va1 75	Thr	Val	Val	Tyr	G1n 80
Asn	Gly	Leu	Pro	Va1 85	Ile	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	G1u 95	Arg
Cys	Gln	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
Arg	Gln	Leu 115	Gln	Glu	Glu	Asp	Arg 120	Gly	Пe	Asp	Arg	Val 125	Ala	Ile	Tyr
	130	•	. •		ŭ	135				Thr	140		•		
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				165	•				170	Glu				175	
	•		180					185		Tyr			190	•	
		195					200			Leu		205			
	210					215				Lys	220	•			
225					230	-				Va1 235		·	-		240
				245			_		250	Ala	_			255	•
			260					265		Thr			270		
		275				-	280	•		Val		285			
	290					295	·			Tyr	300				
305					310			•		G1u 315			Asn	Gln	Leu 320
Lys	Asp	Ala	Пe	A1a 325	Gln	Gln	Lys	Trp	Thr 330	Leu	Arg	Asp			

WO 01/29221

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_		-				aga Arg 55							_	-		192
			-			tgc Cys								-		240
	-	-		_		aca Thr				-	-			-	-	288
				-		tat Tyr	-	-		-			-			336
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Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys	Lys	Leu 125	Met	Cys	Cys	
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	atg Met	Glu			_											576
_	ttc Phe				_	•	•	_	-						-	624
	cnt Xaa 210		_			-	_									672
	ctt Leu	-					_							_		720
	ttc Phe			_	-			_	-		-		-		-	768
	ccc Pro			Lys			-									816
	tcc Ser															864
ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

Leu	His 29 <u>0</u>	Leu	His	Gln	Asn	G1y 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly	
ccc Pro 305	cag Gln	tca Ser	gga Gly	acc Thr	aac Asn 310	aag Lys	cca Pro	agg Arg	gaa Glu	acc Thr 315	tgc Cys	cag Gln	ggc Gly	cct Pro	gag G1u 320	960
tgt Cys	cct Pro	ggc Gly	ctc Leu	cac His 325	acg Thr	ttt Phe	ctc Leu	ttg Leu	tgg Trp 330	tcc Ser	cat His	tca Ser	ggc Gly	ttt Phe 335	aac Asn	1008
tgc Cys	ctg Leu	ctt Leu	tgt Cys 340	gca Ala	gag Glu	atg Met	ctg Leu	gga Gly 345	cgg Arg	aaa Lys	gag Glu	gac Asp	ctc Leu 350	ctc Leu	cac His	1056
cac His	tgg Trp	aag Lys 355	cac His	cag Gln	cat His	aac Asn	tgt Cys 360	gag Glu	gac Asp	cct Pro	tcc Ser	aaa Lys 365	ctg Leu	tgg Trp	gct Ala	1104
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Leu	Thr	Pro	20 Lys	Tyr	Leu	Gly	Cys		Glr	Asp	Asr	ser		Ser	Pro	

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Trp 65	His	Arg	Cys	His	Val 70	Cys	Asn	His	His	Phe 75	Gln	Phe	Lys	Gln	His 80
Leu	Arg	Asp	His	Met 85	Asn	Thr	His	Thr	Asri 90	Arg	Arg	Pro	Tyr	Ser 95	Cys
Arg	Ile	Cys	Arg 100	Lys	Ser	Tyr	Val	Arg 105	Pro	Gly	Ser	Leu	Ser 110	Thr	His
Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys.	Lys	Leu 125	Met	·Cys	Cys
Glu	Phe 130	Cys	Ala	Lys	Val	Phe 135	Gly	Hịs	Пe	Arg	Val 140	Tyr	Phe	Gly	His
Leu 145	Lys	Glu	Val	His	Arg 150	Val	Val	Ile	Ser	Thr 155	Glu	Pro	Ala	Pro	Ser 160
Glu	Leu	Gln	Pro	Gly 165	Asp	Пe	Pro	Lys	Asn 170	Arg	Asp	Met	Ser	Val 175	Arg
Gly	Met	Glu	Gly 180	Ser	Leu	Glu	Arg	G1u 185	Asn	Lys	Ser	Asn	Leu 190	Glu	Glu
Asp	Phe	Leu 195	Leu	Asn	Gln	Ala	Asp 200	Glu	Val	Lys	Leu	G1n 205	Ile	Lys	Cys
Gly	Xaa 210	Cys	Gln	Пe	Thr	Ala 215	Gln	Ser	Phe	Ala	G1u 220	He	Lys	Phe	His
Leu 225	Leu	Asp	Val	His	Gly 230	Glu	Glu	Ile	Glu	Gly 235	Arg	Leu	Gln	Glu	Gly 240
Thr	Phe	Pro	Gly	Ser 245	Lys	Gly	Thr	Gln	G1u 250	Glu	Leu	Val	Gln	His 255	Ala
Ser	Pro	Asp	Trp 260	Lys	Arg	His	Pro	G1u 265	Arg	Gly	Lys	Pro	G1u 270	Lys	Val
His	Ser	Ser 275	Ser	Glu	Glu	Ser	His 280	Ala	Cys	Pro	Arg	Leu 285	Lys	Arg	Gln
Leu	His 290	Leu	His	Gln	Asn	Gly 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly
Pro 305	Gln	Ser	Gly	Thr	Asn 310	Lys	Pro	Arg	Glu	Thr 315	Cys	G1n	Gly	Pro	G1u 320
Cys	Pro	Gly	Leu	His 325	Thr	Phe	Leu	Leu	Trp 330	Ser	His	Ser	Gly	Phe 335	Asn
Cys	Leu	Leu	Cys 340	Ala	Glu	Met	Leu	Gly 345	Arg	Lys	Glu	Asp	Leu 350	Leu	His
His	Trp	Lys 355	His	Gln	His	Asn	Cys 360	Glu	Asp	Pro	Ser	Lys 365	Leu	Trp	Ala
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183

385

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		_					-		-		gaa Glu		384
											ttg Leu	_	432
				_			-		_		ttt Phe		480
				-	_		-				aga Arg 175		528
											cat His		576
-			•	_	-		-	_			gtt Val	_	624
				_	_	_			_	_	ttt Phe		672
											aat Asn	_	720
											aaa Lys 255		768
				-	-	-					aaa Lys		816
				-						-	gat Asp	-	864

			gct Ala						_					_	•	912
			aaa Lys	_	-		-				_					960
			gtg Val		_	_							_		_	1008
			aca Thr 340	-	_							-			_	1056
		_	aat Asn	_			-		_		-		•			1104
	_		aat Asn	-	-		_	_			_	-	-			1152
_	-		aac Asn			-	-	-		_	-					1200
			cct Pro													1248
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-	-	_	tta Leu							_	-		-	_		1344
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				_	-	aat Asn			_				_			1440
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	_	_				aca Thr	-		_		_	-			_	1536
				_	_	agc Ser	-	-								1584
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_			_		-	act Thr		_		-	-	_				1680
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						agc Ser 615										1872
						gaa Glu										1920

		-	att Ile								-					1968
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cct Pro	tga *			•												2022
		•														
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Asn	Glu	Tyr	Asp 180	Leu	Пe	Leu	Asn	Ser 185	Asp	Ile	Asn	Ser	Asn 190	His	Tyr
His	Gl'n	Trp 195	Phe	Tyr	Phe	Glu	Val 200	Ser	Gly	Met	Arg	Pro 205	Gly	Val	Ala
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•		275		Thr			280					285	•	•	
	290			Tyr		295		•		•	300				
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		·		Leu 325					330					335	
•			340	Ala				345		_	-		350		·
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	370			Ala		375					380				
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		-					-	atc Ile			_	-				144

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Ser	Tyr 50		Gly	Пe	Leu	Leu 55		Пе	Thr	Asn	Thr 60		Ala	Thr	Ile	
Pro 65	Gly	Met	Val	Gly	Pro 70	Val	Ile	Ala	Lys	Ser 75	Leu	Thr	Pro	Asp	Asn 80	
	Val	Gly	Glu	Trp 85		Thr	Val	Phe	Tyr 90		Ala	Ala	Ala	11e 95		
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_						ggc Gly									-	528
-				-	-	acg Thr	-									576
_						cct Pro	-	-			-					624
_	_		-			cgc Arg 215										672
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_	_	_		-	_	tct Ser	Pro	Ala						_		768
_			-			gta Val										816
-		-		-		act Thr	-	_								864
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Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Пe	Thr	Glu	
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	cgt Arg				_	_										1008
-	agt Ser	_		_	-	_	_	_		_				_		1056
	tat Tyr													_	_	1104
	tcc Ser 370															1152
	tca Ser		-		-	_	-			_		_				1200
	ttg Leu				-		_							_		1248
	ttc Phe	-				_			_			_		_		1296
	cag Gln					-	-		_	-				-		1344
	ggc Gly 450							_	-	_	-		_		-	1392
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                                        475
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Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met
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Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu
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Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile
Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr
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            100
                                                    110
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                                                125
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                        135
Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile
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Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu
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Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val
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Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val
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195

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Val	Leu 210	Val	Ala	Arg	Gly	Arg 215	Thr	Thr	Asn	Glu	G1n 220	Val	Thr	Gly	Lys
Phe 225	Arg	Gly	Gly	Val	Asn 230	Pro	Phe	Thr	Asn	Gly 235	Cys	Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245	Ser	Ser	Pro	Ala	Pro 250	Arg	Tyr	Leu	Gly	Arg 255	Pro
Lys	Lys	Gļu	Lys 260	Thr	Пe	Val	He	Arg 265	Pro	Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	Пе	Thr	Val 280	Lys	Ile	Met	Asp	Asn 285	Gly	IJе	Gln
Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	He	Thr	Glu
Ser 305	Gln	Ser	Ala	Asp	Ala 310	Glu	Pro	Pro	Pro	Pro 315	Pro	Lys	Pro	Asp	Leu 320
Ser	Arg	Tyr	Thr	Gly 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	Glu
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Sen	Ser 360	Ser	Ser	Thr	Ser	A1 a 365	Ala	Met	Pro
His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	Ile	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	G1u	Pro 400
Ser	Leu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
His	Phe	Asp	Pro 420	Leu	Ser	Ser	Gly	Ser 425	Arg	Ser	Ser	Ser	Leu 430	Lys	Ser
Xaa	Gln	Gly 435	Thr	Gly	Phe	G1u	Leu 440	Gly <sub>.</sub>	Gln	Leu	Gln	Ser 445	Ile	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	Ala 460	Asn	Gln	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
Asp	Phę	Glu	Ser	Va1 485	Gln	Ala	Gly	Leu	Ser 490	Gln	Thr	His	Leu		

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<212> DNA

<213> Homo sapiens

<220>

196

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gac tga Asp \* 246

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<212> PRT

<213> Homo sapiens

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Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp 35 40 45

Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr 50 55 60

Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Gln Arg Thr Leu

65 Asp	٠.				70					75				80	
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						gct Ala					-				96
					-	gcg Ala			_	_	_				144
						aaa Lys 55									192
				_		gcg Ala				_					240
						att Ile		_	_	_	_	 -	_	tct Ser	288
	-					ttc Phe	_	_	-			 _	_	•	336
						ctg Leu	-			_	_		-	-	384

		115					120					125				
									aca Thr						_	432
									gtg Val							480
					Leu				cag Gln 170						_	528
			ctg Leu 180			aga Arg	tag *									552
	<; <;	210> 211> 212> 213>	183	o sar	oiens	5										
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Leu	Ala	Ala	G1n 20	Pro	Pro	Ala	Ala	Ser 25	Gln	Gly	Ala	Gln	Thr 30	Pro	Gly	
Glu	Lys	A1a 35	Glu	Ala	Ala	Ala	Thr 40	Leu	Lys	Ala	Ala	Pro 45	Gly	Trp	Leu	
	Arg .50	Phe	Leu	Val	Trp	Lys 55	Pro	Arg	Pro	Ala	Ser 60	Ala	Arg	Ala	Gln	
		Leu	Val	Gln	G1u 70		Ala	Gln	Pro	G1n 75		Ser	Thr	Ser	Glu 80	
	Pro	Trp	Asn	Thr 85		Ile	Pro	Leu	Pro 90		Cys	Trp	Asp	G1n 95		
Phe	Leu	Thr	Asn 100		Thr	Phe	Leu	Lys 105	Val	Leu	Leu	Trp	Leu 110		Leu	
Leu	Gly	Leu 115		Val	Glu	Leu	G1u 120		Gly	Leu	Ala	Tyr 125		Val	Leu	
Ser	Leu 130		Tyr	Trp	Met	Tyr 135		Gly	Thr	Arg	Gly 140		Glu	Glu	Lys	
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-			-								-		tct Ser		_	192
	-		_	_		_	-	_	_		Phe	_	atg Met			240
_			_									_	tca Ser			288
-	_				-	_	_		-		-	_	agt Ser 110	_	-	336

						agc Ser										384
				-		cct Pro 135								-		432
		-				aac Asn	-			-			-			480
	-		_	_	-	gct Ala	-		_			-	-		_	528
			_			ctg Leu	-		-			_		_	• •	576
						ccg Pro	-		-							624
-	-		-	-	_	aga Arg 215		-	-						•	672
	-	-			-	ctg Leu			_				-	-	_	720
						aac Asn									cag · Gln	768
			-	_	_	tca Ser				_	_	_		_	-	816
		_	-	_		gaa Glu	-			-	_	_	-	_		864

201

912

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Trp	Gly		260 Lys	Glu	Val	Glu		265 His	Tyr	Cys	Asp		270 Cys	Gln	Phe	
Ser	Asn 290	275 Arg	Phe	Pro	Arg	Trp 295	280 Val	Pro	Trp	Met	Val 300	285 Lys	Ser	Glu		
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		_				-	-	-			-	-		ctt Leu	-	192
														att Ile		240
									-	-			_	aac Asn 95		288
											-	-		aaa Lys		336

				_	agt Ser					-			_		aat Asn	384
	-	-			gtt Val	-				-		_			-	432
					aat Asn 150											480
			-		gtg Val									-	_	528
	-	-	_		att Ile			_	-		•			_		576
	•		_		aaa Lys		-				_		_			624
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<211> 249

<212> PRT

<213> Homo sapiens

<400> 142

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Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40	Arg	Ser	Ser	Lys	Ser 45	Ala	Glu	Asp
Leu	Thr 50	Asp	Gly	Ser	Tyr	Asp 55	Asp	Val	Leu	Asn	Ala 60	Glu	G1n	Leu	Gln
Lys 65	Leu	Leu	Tyr	Leu	Leu 70	Glu	Ser	Thr	Glu	Asp 75	Pro	Val	Ile	Ile	G1u 80
Arg	Ala	Leu	Ile	Thr 85	Leu	Gly	Asn	Asn	A1a 90	Ala	Phe	Ser	Val	Asn 95	Gln
Ala	Ile	He	Arg 100	Glu	Leu	Gly	Gly	Ile 105	Pro	Ile	Val	Ala	Asn 110	Lys	Пe
Asn	His	Ser 115	Asn	Gln	Ser	Ile	Lys 120	Glu	Lys	Ala	Leu	Asn 125	Ala	Leu	Asn
	130					135		Gln			140				
145					150			Glu		155					160
Leu	Leu	Arg	Ala	G1n 165	Val	Asp	Ser	Ser	Phe 170	Leu	Ser	Leu	Tyr	Asp 175	Ser
			180					Arg 185					190		
He	Lys	Asn 195	Cys	Leu	Lys	Пe	G1u 200	Gly	His	Leu	Ala	Val 205	Gln	Pro	Thr
Phe	Thr 210	Glu	Gly	Ser	Leu	Phe 215	Phe	Leu	Leu	His	G1y 220	Glu	Glu	Cys	Ala
225			_		230		•	His	His	Asp 235	Ala	Glu	Val	Lys.	G1u 240
Lys	Val	Val	Thr	I 1e 245	Пe	Pro	Lys	Ile							
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<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(846)

<221> misc\_feature

<222> (1)...(846)

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		-	cct Pro	-	_	-	_				-				.144
		_	ggc Gly	 _	_	_	_				_	-		-	192
			tcc Ser			-		-			- ,			-	240
-		_	gca Ala	 	-		-		-			-	-	_	288
			tgg Trp 100	-		-			_			-	_		336
	-		gac Asp	•			-	-		-	_	-		_	384
			999 Gly												432
			gtg Val										_		480
			tcc Ser												528

206

165 170 175 gat ggg ttg ttg ggc tcc ccg gcc cgg ctg gcc tcc cag ctg ctg ggc 576 Asp Gly Leu Leu Gly Ser Pro Ala Arg Leu Ala Ser Gln Leu Leu Gly 180 185 190 gat gag ctg ctt ctc gcc aaa ctg ccc ccc agc cgg gaa agt gcc ttc 624 Asp Glu Leu Leu Leu Ala Lys Leu Pro Pro Ser Arg Glu Ser Ala Phe 195 200 cgc agc ctg ggc cca ctg gag gcc cag gac tca ctc tac aac tcg ccc 672 Arg Ser Leu Gly Pro Leu Glu Ala Gln Asp Ser Leu Tyr Asn Ser Pro 210 215 220 ctc aca gag tee tgc ett tee eee geg gag gag gag eea gee eee tge 720 Leu Thr Glu Ser Cys Leu Ser Pro Ala Glu Glu Glu Pro Ala Pro Cys 225 230 235 240 aag gac tgc cag cca ctc tgc cca cca cta acg ggc agc tgg gaa cgg 768 Lys Asp Cys Gln Pro Leu Cys Pro Pro Leu Thr Gly Ser Trp Glu Arg 245 250 cag cgg caa gcc tct gac ctg gcc tct tct ggg gtg gtg tcc tta gat 816 Gln Arg Gln Ala Ser Asp Leu Ala Ser Ser Gly Val Val Ser Leu Asp 260 265 270 gag gat gag gca gag cca gag gaa cag tga 846 Glu Asp Glu Ala Glu Pro Glu Glu Gln \* 275 280 <210> 144 <211> 281 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(281) <223> Xaa = Any Amino Acid <400> 144 Met Leu Pro Lys Ser Arg Arg Ala Leu Thr Ile Gln Xaa Ile Ala Ala 5 1 10 15

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Val	Thr	Lys 35	Pro	Thr	Ala	Met	Ala 40	Gln	Gly	Arg	Val	Ala 45	His	Leu	Ile
Glu	Trp 50	Lys	Gly	Trp	Ser	Lys 55	Pro	Ser	Asp	Ser	Pro 60	Ala	Ala	Leu	Glu
Ser 65	Ala	Phe	Ser	Ser	Tyr 70	Ser	Asp	Leu	Ser	Glu 75	Gly	Glu	Gln	Glu	A1a 80
Arg	Phe	Ala	Ala	Gly 85	Val	Ala	Glu	Gln	Phe 90	Ala	IJе	Ala	Glu	Ala 95	Lys
Leu	Arg	Αla	Trp 100	Ser	Ser	Val	Asp	Gly 105	Glu	Asp	Ser	Thr	Asp 110	Asp	Ser
Tyr	Asp	Glu 115	Asp	Phe	Ala	_	Gly 120	Met	Asp	Thr	Asp	Met 125		Gly	Gln
Leu	Pro 130	Leu	Gly	Pro	His	Leu 135	Gln	Asp	Leu	Phe	Thr 140	Gļy	His	Arg	Phe
Ser 145	Arg	Pro	Val	Arg	Gln 150	Gly	Ser	Val	Glu	Pro 155	Glu	Ser	Asp	Cys	Ser 160
Gln	Thr	Val	Ser	Pro 165	Asp	Thr	Leu	Cys	Ser 170	Ser	Leu	Cys	Ser	Leu 175	
Asp	Gly	Leu	Leu 180	Gly	Ser	Pro	Ala	Arg 185	Leu	Ala	Ser	Gln	Leu 190	Leu	Gly
Asp	Glu	Leu 195	Leu	Leu	Ala	Lys	Leu 200	Pro	Pro	Ser	Arg	G1u 205	Ser	Ala	Phe
Arg	Ser 210	Leu	Gly	Pro	Leu	G]u 215	Ala	Gln	Asp	Ser	Leu 220	Tyr	Asn	Ser	Pro
Leu 225	Thr	Glu	Ser	Cys	Leu 230	Ser	Pro	Ala	Glu	G1u 235	Glu	Pro	Ala	Pro	Cys 240
Lys	Asp	Cys	Gln	Pro 245	Leu	Cys	Pro	Pro	Leu 250	Thr	Gly	Ser	Trp	G1u 255	Arg
Gln	Arg	Gln	Ala 260	Ser	Asp	Leu	Ala	Ser 265	Ser	Gly	Val	Val	Ser 270	Leu	Asp
G1u	Asp	G1u 275	Ala	Glu	Pro	Glu	G1u 280	Gln							
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												tat Tyr			144
		_	-	-	_	-						tac Tyr			192
			_					_	-			gcc Ala			240
	_	-			-			-				gtg Val	-		288
			-		_		Arg			_	_	ctc Leu 110			336
-					-	-						gac Asp			384
					_	_						gcc Ala			432
												gaa Glu			480
_			Ă٦a					-		-	_	gct Ala	-		528

				_	-					gtg Val			-	-	-	576
-					_					ccc Pro				-		624
		-	_	_	_		-		-	ctt Leu						672
		_		_	_	_				acc Thr 235		-			-	720
_			-		-	_	-		_	ctg Leu						768
-				-	-					gtc Val						816
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•	-	_	_	_					_	tac Tyr	-		-			912
-					_		_			ctg Leu 315			-		ctc Leu 320	960
	-	-					-	•		ttc Phe			-			1008
-	-	-	_	-					_	ttt Phe					_	1056

-	tgt Cys						_						_	-		1104
	cct Pro 370				-	-		-						-		1152
-	cac His		•	•	_					_			-	-	-	1200
-	aaa Lys						-		-				-	-	-	1248
	atg Met	-	_	_	-										cat His	1296
-	gct Ala		-		-									_		1344
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Leu	Gly	Leu	G1u 20	Leu	Ser	Arg	Cys	Arg 25	Ala	Lys	Pro	Pro	G1y 30	Arg	Ala	
Cys	Ser	Asn 35		Ser	Phe	Leu	Arg 40	-	Gln	Leu	Asp	Phe 45		Gln	Val	
Tyr	Phe 50		Ala	Leu	Ala	Ala 55		Trp	Leu	Gln	A1a 60		Tyr	Leu	Tyr	

Lys 65	Leu	Tyr	Gln	His	Tyr 70	Tyr	Phe	Leu	Glu	Gly 75	Gln	Ile	Ala	Пe	Leu 80
Tyr	Val	Cys	Gly	Leu 85	Ala	Ser	Thr	Val	Leu 90	Phe	Gly	Leu	Val	Ala 95	Ser
Ser	Leu	Val	Asp 100	Trp	Leu	Gly	Arg	Lys 105	Asn	Ser	Cys	Val	Leu 110	Phe	Ser
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Val	Leu 130	Leu	Val	Gly	Arg	Ala 135	Leu	Gly	Gly	Leu	Ser 140	Thr	Ala	Leu	Leu
Phe 145	Ser	Ala	Phe	Glu	Ala 150	Trp	Tyr	Ile	His	Glu 155	His	Val	Glu	Arg	His 160
Asp	Phe	Pro	Ala	Glu 165	Trp	Ile	Pro	Ala	Thr 170	Phe	Ala	Arg	Ala	Ala 175	Phe
Trp	Asn	His	Val 180	Leu	Ala	Val	Val	Ala 185	Gly	Val	Ala	Ala	Glu 190	Ala	Val
Ala	Ser	Trp 195	Ile	Gly	Leu	Gly	Pro 200	Val	Ala	Pro	Phe	Va1 205	Ala	Ala	Ile
Pro	Leu 210	Leu	Ala	Leu	Ala	Gly 215	Ala	Leu	Ala	Leu	Arg 220	Asn	Trp	Gly	Glu
225		·			230				Arg	235			-	_	240
Arg	Cys	Leu	Leu	Ser 245	Asp	Arg	Arg	Val	Leu 250	Leu	Leu	Gly	Thr	11e 255	Gln
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	Val	Val	Phe	Ser 325	310 Leu	Pro Phe	Met	Leu	Thr 330	315 Phe	Ser Ser	Thr	Ser	Pro 335	320 Gly
Gln	Val Glu	Val Ser	Phe Pro 340	Ser 325 Val	310 Leu Glu	Pro Phe Ser	Met Phe	Leu Ile 345	Thr 330 Ala	315 Phe Phe	Ser Ser Leu	Thr Leu	Ser Ile 350	Pro 335 Glu	320 Gly Leu
Gln	Val Glu	Val Ser	Phe Pro 340	Ser 325 Val	310 Leu Glu	Pro Phe Ser	Met Phe	Leu Ile 345	Thr 330	315 Phe Phe	Ser Ser Leu	Thr Leu	Ser Ile 350	Pro 335 Glu	320 Gly Leu
Gln Ala Ile	Val Glu Cys Pro 370	Val Ser Gly 355 Glu	Phe Pro 340 Leu Thr	Ser 325 Val Tyr Glu	310 Leu Glu Phe Gln	Pro Phe Ser Pro Ala 375	Met Phe Ser 360 Gly	Leu Ile 345 Met	Thr 330 Ala Ser Leu	315 Phe Phe Phe Asn	Ser Ser Leu Leu Trp 380	Thr Leu Arg 365 Phe	Ser Ile 350 Arg	Pro 335 Glu Lys Val	320 Gly Leu Val Pro
Gln Ala Ile Leu 385	Val Glu Cys Pro 370 His	Val Ser Gly 355 Glu Ser	Phe Pro 340 Leu Thr	Ser 325 Val Tyr Glu Ala	310 Leu Glu Phe Gln Cys 390	Pro Phe Ser Pro Ala 375 Leu	Met Phe Ser 360 Gly Gly	Leu Ile 345 Met Val Leu	Thr 330 Ala Ser	315 Phe Phe Phe Asn Val 395	Ser Ser Leu Leu Trp 380 Leu	Thr Leu Arg 365 Phe His	Ser Ile 350 Arg Arg	Pro 335 Glu Lys Val	320 Gly Leu Val Pro Asp 400

Val	Met	Ala	Leu 420	Leu	Ala	Val	Val	Gly 425	Leu	Phe	Thr	Val	Va1 430	Arg	His	
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Glu	Leu 450															
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						-								aag Lys		144
	-	_					_		_					cga Arg	-	192
					-	_								cag Gln		240
														tgc Cys 95		288

-	-		_			aat Asn	-							Gly	-	336
			-			999 Gly										384
	_				-	cac His 135										432
	-	_		_		tcc Ser										465
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1 Leu	Ala Tyr	Gly Gln	Pro Ala 20	·5 Ala	His	·	Val	Leu 25	10 Ala	Gln	Asp	Pro	G1u 30	15 Asn	Gln	
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PCT/US00/29052

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Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn 50 55 60

Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg 65 70 75 80

Gly Val Val Cys Arg Leu Ser Arg Ser Leu Gln Glu His His Gly Leu 85 90 95

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Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
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223 -

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-	-	-	-	-	-	gca Ala	-							-	-	576
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						cta Leu						-				768

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-		-	-		_	atc Ile		-	-		_		-		•	816
_			-		-	cta Leu	-			-			•	_		864
			-			agg Arg 295		-				_	-	-	-	912
_					_	ctt Leu			_	-		_		_	-	960
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Leu	His 290	Asn	Glu	Ile	Thr	Arg 295	Thr	Leu	Glu	Lys	Ile 300	Ser	Ser	Arg	Glu	
Lys 305	Tyr	Ile	Asn	Asn	Gln 310	Leu	Glu	Asn	Leu	Val 315	Gln	Glu	Tyr	Arg	A1a 320	
	Gln	Ala	Gln	Leu 325		Glu	Ala	Lys	G1u 330		Tyr	Gln	Gln	Gly 335		
Gly	Gly	Val	Thr 340		Arg	Thr	Arg	Leu 345		Ser	Glu	Val	Met 350	Glu	Glu	
Leu	Glu	Lys 355		Lys	Gln	Glu	Met 360		Glu	Lys	Gly	Ser 365		Met	Thr	
Asp	Gly 370		Pro	Leu	Val	Lys 375	Пe	Lys	Gln	Ser	Leu 380		Lys	Leu ·	Lys	
G1n 385		Thr	Val	Glu	Met 390		Пe	Arg	He	Gly 395		Val	Glu	His	Thr 400	
	Leu	Gln	Ser	Lys 405	Leu	Lys	Glu	Lys	Ser 410	Asn	Met	Thr	Arg	Asn 415		
His	Ala	Thr	Va1 420	Ile	Pro	Glu	Pro	Ala 425	Thr	Gly	Phe	Tyr				
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999 Gly				_			-	_	-		_			aac		192

			aag Lys										-	_	-	240
			gcc Ala		-	-					_	_				288
	-		ttg Leu 100		_			_				-	-	-	-	336
-	-		aag Lys	_	_		-							-	-	384
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	His	Phe	Asn 20		Gly	Glu	Tyr	Ala 25		A1 a	Glu	Ala	Leu 30		Ser	
Ala	Tyr	Ile 35	Arg	Arg	Cys	Ala	Cys 40		Ala	Ser	Ser	Asp 45		Ser	Pro	
Gly	Ser 50		Cys	Ser	Pro	G1u 55		Leu	Ala	Thr	A1a 60		Asn	Asn	Arg	
Gly 65		Ile	Lys	Tyr	Phe 70		Val	Asp	Phe	Tyr 75		Ala	Met	Asp	Asp 80	
	Thr	Ser	Ala	11e 85	Glu	۷a٦ <sub>.</sub>	Gln	Pro	Asn 90		Glu	Val	Pro	Tyr 95		

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Asn Arg Gly Leu Ile Leu Tyr Arg Leu Gly Tyr Phe Asp Asp Ala Leu 100 105 Glu Asp Phe Lys Lys Val Leu Asp Leu Asn Pro Gly Phe Gln Asp Ala 120 Thr Leu Ser Leu Lys Gln Thr Ile Leu Asp Lys Glu Glu Lys Gln Arg 140 135 Arg Asn Val Ala Lys Asn Tyr 145 150 <210> 165 <211> 1032 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1032) <400> 165 atg atg ctg ctc tat gaa gaa ggc ctc cgg gtt gtc ata cac acc 48 Met Met Leu Leu Leu Tyr Glu Glu Gly Leu Arg Val Val Ile His Thr 1 5 10 15 tcc aac ctc atc cat gct gac tgg cac cag aaa act caa gga ata tgg 96 Ser Asn Leu Ile His Ala Asp Trp His Gln Lys Thr Gln Gly Ile Trp 20 ttg agc ccc tta tac cca cga att gct gat gga acc cac aaa tct gga 144 Leu Ser Pro Leu Tyr Pro Arg Ile Ala Asp Gly Thr His Lys Ser Gly 35 40 45 gag tcg cca aca cat ttt aaa gct gat ctc atc agt tac ttg atg gct 192 Glu Ser Pro Thr His Phe Lys Ala Asp Leu Ile Ser Tyr Leu Met Ala 50 tat aat gcc cct tct ctc aag gag tgg ata gat gtc att cac aag cac 240 Tyr Asn Ala Pro Ser Leu Lys Glu Trp Ile Asp Val Ile His Lys His 65 70 75 80 288 gat ctc tct gaa aca aat gtt tat ctt att ggt tca acc cca gga cgc Asp Leu Ser Glu Thr Asn Val Tyr Leu Ile Gly Ser Thr Pro Gly Arg 85 90 95 336 ttt caa gga agt caa aaa gat aat tgg gga cat ttt aga ctt aag aag

Phe	G1n	Gly	Ser 100	Gln	Lys	Asp	Asn	Trp 105	Gly	His	Phe	Arg	Leu 110	Lys	Lys	
			gac Asp		-						_					384
-			cag G1n			_	-					-	-	_		432
			tgt Cys							_	_		-		_	480
		-	act Thr				_		_				_			528
			gaa Glu 180											-		576
			ccc Pro									_			-	624
			ttt Phe													672
			cat His		_			_					_		_	<sup>-</sup> 720
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gag	ctc	999	gtc	cťt	ttc	ctc	cct	tca	gca	ttt	ggt	cta	gac	agt	ttc	864

Glu	Leu	Gly 275	Val	Leu	Phe	Leu	Pro 280	Ser	Ala	Phe	Gly	Leu 285	Asp	Ser	Phe	
	gtg Val 290		_	_			-		-	-			_	•		912
	cct Pro				_	_			_	_			_		-	960
	cca Pro								-		-	-	-	-		1008
	aac Asn						tga *									1032
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Ser	Asn	Leu	Ile 20	His	Ala	Asp	Trp	His 25	Gln	Lys	Thr	Gln	Gly 30	Ile	Trp	
Leu	Ser	Pro 35	Leu	Tyr	Pro	Arg	Ile 40	Ala	Asp	Gly	Thr	His 45	Lys	Ser	Gly	
Glu	Ser 50	Pro	Thr	His	Phe	Lys 55	Ala	Asp	Leu	Ile	Ser 60	Tyr	Leu	Met	Ala	
Tyr 65	Asn	Ala	Pro	Ser	Leu 70	Lys	Glu	Trp	Ile	Asp 75	Val	He	His	Lys	His 80	
Asp	Leu	Ser	Glu	Thr 85	Asn	Val	Tyr	Leu	Ile 90	Gly	Ser	Thr	Pro	Gly 95	Arg	
Phe	Gln	Gly	Ser 100		Lys	Asp	Asn	Trp 105		His	Phe		Leu 110		Lys	
						C	Sar		Pro	Asn	Ala			Trn	Pro	
Leu	Leu	Lys 115	Asp	His	Ala	ser	120	1100		, , , , , ,	,,,,	125	00,	P	110	

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Lys 145	irp	Leu	Cys	Ser	150	Pne	Lys	GIU	5er	тет 155	Leu	ınr	Leu	Gly	Lys 160	
	Ser	Lys	Thr	Pro 165		Lys	Ser	Ser	Val 170		Leu	Tyr	Leu	Ile 175		
Pro	Ser	Val	Glu 180		۷a۱	Arg	Thr	Ser 185		Glu	Gly	Tyr	Pro 190		Gly	
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His	Ser 210		Phe	His	Lys	Trp 215		Ala	Glu	Thr	Ser 220		Arg	Ser	Asn	
Ala 225		Pro	His	Ile	Lys 230		Tyr	Met	Arg	Pro 235		Pro	Asp	Phe	Ser 240	
	Ile	Ala	Trp	Phe 245		Val	Thr	Ser	Ala 250		Leu	Ser	Lys	A1 a 255		
Trp	Gly	Ala	Leu 260		Lys	Asn	Gly	Thr 265		Leu	Met	Пe	Arg 270		Tyr	
Glu	Leu	G1y 275		Leu	Phe	Leu	Pro 280	Ser	Ala	Phe	Gly	Leu 285	Asp	Ser	Phe	
Lys	Val 290	Lys	Gln	Lys	Phe	Phe 295	Ala	Gly	Ser	Gln	G1u 300	Pro	Met	Ala	Thr	
Phe 305	Pro	Val	Pro	Tyr	Asp 310	Leu	Pro	Pro	Glu ·	Leu 315	Tyr	Gly	Ser	Lys	Asp 320	
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-	_	_			acc Thr	-		_	-	-		_	_	•	240
		_			gca Ala			-		-					288
_	_	 -	_		acc Thr		-	_			_		_	•	336
		_		_	cag Gln	_		_	-			_		_	384
					atc Ile 135										432
_	_		-		cct Pro	-			-				_		480
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Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala
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                                        75
Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
                                105
Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
        115
                            120
Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
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Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
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	_		ctg Leu	_	-	-						-				192
			ctt Leu		_			-				_	_	-		240
_	-		aac Asn	-		-		_	-	_		-				288
			tca Ser 100				_				-	-			-	336
			cca Pro		-	-	_		_	-		-	-			384
			act Thr											_		432
			ctc Leu													480 <sup>-</sup>
			ggt Gly					_	_						_	528

			_	-					-					atg Met		576
		_				_			_	_			_	cta Leu	-	624
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Mak		100>		1	۸7.	1	71.	1	N.J	C1	112 -	V-1	,	1	1 -	
met 1	arg	Val	ыу	Leu 5	Ald	Leu	rie	Leu	10	ыу	HIS	vai	ASN	Leu 15	Leu	
Leu	Gly	Ala	Val 20	Leu	His	Gly	Thr	Val 25	Leu	Arg	His	Val	Ala 30	Asn	Pro	
Arg	Gly	A1a 35	Val	Thr	Pro	Glu	Tyr 40		Val	Ala	Asn	Val 45		Ser	Val	
Gly	Ser 50		Leu	Leu	Ser	Va1 55		Val	Gly	Leu	Va1 60		Leu	Leu	Ala	
Ser 65		Asn	Leu	Leu	Arg 70		Pro	Leu	His	Trp 75		Leu	Leu	Ala	Leu 80	
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Asp	Cys	His 115		Gly	Leu	Leu	Asp 120		Leu	Val	Pro	Leu 125		Glu	Gly	
Pro	Gly 130	His	Thr	Asp	Cys	Pro 135	Phe	Asp	Pro	Thr	Arg 140		Tyr	Asp	Thr	
		Ala	Leu	Trp			Ser	Leu	Leu			Ala	Gly	Glu		
145 Ala	Leu	Ser	Gly		150 Cys	Cys	Val	Ala		155 Leu	Thr	Leu	Arg	Gly	160 Val	
Gly	Pro	Cys	Arg 180	165 Lys	Asp	Gly	Leu	Gln 185	170 Gly	Gln	Leu	Glu	Glu 190	175 Met	Thr	

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	att Ile														-	240
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Leu Gln Tyr Leu Phe Glu Asn Ile Ser Gln Leu Thr Glu Lys Asp Val 35 40 45

Ser Thr Thr Val Ser Arg Lys Ala Trp Gly Ala Glu Ala Val Gly Cys 50 55 60

Ser Ile Gln Leu Thr Thr Pro Val Asn Val Leu Val Ile His His Val 65 70 75 80

Pro Gly Leu Glu Cys His Asp Gln Thr Val Cys Ser Gln Arg Leu Arg
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Glu Leu Gln Ala His His Val His Asn Asn Ser Gly Cys Asp Val Ala 100 105 110

Tyr Lys

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												gag Glu		144
					_						_	aaa Lys		192
	 _						-				-	tgg Trp	_	240
					_							ggc Gly 95	-	288
	 				_	_	_	_	_	 -		ctg Leu		336
-	_	_		_	_	_					-	tcg Ser		384
				-		-						atg Met		432
	 -	-	_	_			-	-	-		-	ctg Leu	-	480
												cac His 175		528
												ccc Pro		576
												aag Lys		624

												•				
				-	_	_			_				_	gtg Val		672
	_			-		_							_	agt Ser		720
-			_	_	-	-	_	_			-	•	-	gtg Val 255		768
		-	_	_			-							gtg Val	-	816
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		_		_	_	-		_	_					atc Ile		912
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His	Ala	Leu 35		Val	Val	Asn	Met 40		Пе	Thr	Glu	His 45		Glu	Asn	
Phe	Asn 50		Met	Phe	Thr	Lys 55		Lys	Leu	Glu	Gln 60		Leu	Lys	Gly	

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295

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	_		-											tcc Ser	_	144
-												-		aca Thr		192
				_								-	-	tca Ser	-	240
	-			_	_			-					-	tct Ser 95		288
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_							_	-		_				cag G1n		384
				_		-				-				tct Ser	-	432
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gga	tca	aaa	ttt	gat	act	<b>9</b> 99	agc	ttt	gtt	ggt	ggt	att	gta	tta	acg	528

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						_							gcc Ala			624
taa *																627
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Met 1	<	223> <b>4</b> 00>	(1) Xaa 176	(2 = Ar Ala	ny An				Ala 10	Ala	Leu	Leu	Leu	Gly 15	Thr	
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1 Leu	<td>223&gt; 400&gt; Leu Va1</td> <td>(1) Xaa 176 Gly Leu 20</td> <td>Ala 5 Ala</td> <td>Arg Leu</td> <td>Gly Leu</td> <td>Ala Gly</td> <td>Trp Ala 25</td> <td>10 Ala</td> <td>His</td> <td>Glu</td> <td>Ser</td> <td>Ala</td> <td>15 Xaa</td> <td>Met</td> <td></td>	223> 400> Leu Va1	(1) Xaa 176 Gly Leu 20	Ala 5 Ala	Arg Leu	Gly Leu	Ala Gly	Trp Ala 25	10 Ala	His	Glu	Ser	Ala	15 Xaa	Met	
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Gly	Ser	Lys	Phe	•	Thr	Gly	Ser	Phe		Gly	Gly	He	Val	Leu	Thr	
1	C1	V-1	1	165	77_		T	T3_	170	C	1	Mak	т	175	<b>C</b> .	
Leu	ыу	vai		Ser	He	Leu	ıyr	11e 185	GIY	Lys	Lys	met	_	Tyr	Ser	
۸ra	Δra	GIV	180	۸ra	Tyr	۸ra	Thr		۸cn	Glu	Hic	Asn	190	Пe	Ha	•
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1		·		5		-			10					15		
									,							0.5
-	-			_	-					-		-		gtc	_	96
Cys	ASP	arg	20	vai	vai	ASTI	ыу	25	116	Ald	ını.	Val	30	Val	5er	
			20					23					50			
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				-	_			-					-	Phe	-	
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Pro		Gly	Gly	Lys	мет		Pro	lyr	Ser	Ser		Gly	Pro	Ser	HIS	
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-	-	-		-		-	_						_	Thr	_	•
65	•			•	70			•		75	-		-		80	

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											gag Glu		336
											att Ile		384
		-		_		_	_				aac Asn		432
									_		cag G1n	_	480
		_	_	-		-				-	cag Gln 175		528
									-		ccc Pro		576
				 	_	_	_	_	-	_	acc Thr		624
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											gtc Val		720
											gat Asp 255		768

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				-						gag Glu				-	864
-			-	-	-	_	_		-	ggt Gly			-	•	912
_		-			_				-	999 Gly 315	_	_		_	960
	-		•		-			•	-	ata Ile	 		•		1008
				-	-	_		-		atg Met	-	_	_		1056
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	-	_	_	_			_	-		atc Ile			_	•	1152
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										tgc Cys			-		1248
										ctg Leu					1296

WO 01/29221 PCT/US00/29052

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	aac Asn	tga *														1401
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1 Cys	Asp	Arg Ile	Thr 20	Val			Val	25	Ile			Ile	30			
1 Cys Trp	Asp Ile Leu	Arg Ile 35	Thr 20 Ile	Val Ala	Ala	Thr Ala	Va1 40	25 Val	Ile Ser	Ile	Ile Ala	Ile 45	30 Val	Val	Asp	
1 Cys Trp Pro Leu	Asp Ile Leu 50	Arg Ile 35 Gly	Thr 20 Ile Gly	Val Ala Lys	Ala Met Ser	Thr Ala 55	Val 40 Pro	25 Val Tyr	Ile Ser Ser	Ile Ser Asn	Ile Ala 60	Ile 45 Gly	30 Val Pro	Val Phe	Asp His Ala	
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Ala	Asp	Leu	Asp	Ala 165	Glu	Leu	Glu	Asn	Cys 170	His	His	Tyr	Met	G1n 175	Phe
Ala	Ala	Ala	Ala 180	Tyr	Gly	Trp	Pro	Leu 185	Tyr	Ile	Tyr	Arg	Asn 190	Pro	Leu
Thr	Gly	Leu 195	Cys	Arg	Ile	Gly	Gly 200	Asp	Cys	Cys	Arg	Ser 205	Arg	Thr	Thr
	Tyr 210	Asp	Leu	Val	Gly	Gly 215	Asp	Gln	Leu	Asn	Cys 220	His	Phe	Gly	Ser
Ile 225	Leu	His	Thr	Thr	Gly 230	Leu	Gln	Tyr	Arg	Asp 235	Phe	Ile	His	Val	Ser 240
Phe	His	Asp	Lys	Va1 245	Tyr	G1.u	Leu	Pro	Phe 250	Leu	Val	Ala	Leu	Asp 255	His
Arg	Lys	Glu	Ser 260	Val	Val	Val	Ala	Va1 265	Arg	Gly	Thr	Met	Ser 270	Leu	Gln
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•	290		Gln	•	_	295			-	_	300				
305			Tyr		310				·	315					320
			Ala	325			_		330			-		335	
_			A1 a 340					345				_	350		
		355	Arg	•	•		360				-	365			
	370		Gln			375					380				
385			Val		390					395					400
-			Ile	405					410			_		415	
Lys	IJе		Leu 420	His	Gly				Glu		Phe		G1 <i>y</i> 430		Pro
Asn	Asn	Leu 435	Pro	Ser	Thr	Arg	G1y 440	Leu	G1n	Cys	Gly	Arg 445	Gly	Leu	Thr
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_			-							-	-	-	-	cta Leu		192
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				-										ctc Leu 95		288
														gta Val		336
_	_				-									gaa Glu		384
tat	gat	tcc	ttt	tca	aat	cga	tgg	act	gaa	gtt	gct	ССС	ctt	aag	gaa	432

Tyr	Asp 130	Ser	Phe	Ser	Asn	Arg 135	Trp	Thr	Glu	Val ·	Ala 140	Pro	Leu	Lys	Glu		
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	_		_		aat Asn					_	_	_					576
					aca Thr		-					-			-		624
_			_		aag Lys	_			-		-		-	•	~	ī	672
				_	cag Gln 230					-				-			720
					ggt Gly					-			-		_		768
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Ile	Пe	Thr 275	Gly	Val	Ala	Ala	Met 280	Pro	Arg	Pro	Val	Ser 285	Tyr	His	Gly	
Cys	Va1 290		Ile	His	Arg	Tyr 295		Glu	Lys	Cys	Phe 300		Leu			
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					gag Glu											192
-					ggc Gly 70			-								240
					gga Gly											288

258

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Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
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                                 105
tgc ccg ccc cct cca gcc tac tgc aac acg cct ccg ccc ccg tac gaa
                                                                      384
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
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                                                 125
cag gta gtg aag gcc aag tag
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Gln Val Val Lys Ala Lys *
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                                                 45
Pro Pro Pro Leu Ile Glu Glu Pro Ala Phe Asn Val Ser Tyr Thr Arg
                        55
Gln Pro Pro Asn Pro Gly Pro Gly Ala Gln Gln Pro Gly Pro Pro Tyr
Tyr Thr Asp Pro Gly Gly Pro Gly Met Asn Pro Val Gly Asn Ser Met
                85
                                    90
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
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Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
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-				_	gat Asp											144
	_		_	_	ctg Leu	_	-	_	_				-			192
			_	-	aac Asn 70				_	-						240
	_		_	-	ctg Leu									-	atg Met	. 288
					ctg Leu											336
		-			att Ile		_									384

	-	_		agc Ser		-					-	_		_	43	12
	_		-	ctg Leu 150	_				-			_	_	•	. 48	0
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				tat Tyr											57	'6
-	-			cag Gln	_	-	_	-		_			_		62	<u>'</u> 4
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			_	 agg Arg 230		_				_			_		. 72	<u>'</u> 0
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	-			 atc Ile		_				<u> </u>					81	6
_				cac His											86	4
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Val	Leu	Thr 275	Leu	Thr	His	Phe	Gly 280	Leu	Leu	Ala	Ser	Pro 285	Phe	Leu	Ser	
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		-			ttt Phe	_	-		_	_				_	_	192
			-		tcc Ser 70	_	_		-	-			_			240
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-		-	-	_	gct Ala		-							_	_	336

263

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														aat Asn		480
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	_			-			_						_	gac Asp		576
-		-					_	_	-		-			cac His		624
														gct Ala		672
	_		_						Asp					gcc Ala	-	720
	-	_												cca Pro 255	-	768
_		-												aag Lys		816
	_		_			-	-		-					gac Asp		864
					-				-	_	_	_		aac Asn		912
• -		_	-	_		-		-	-					act Thr		960

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											gtt Val		-	-		1056
-	-	_	_						_		gaa Glu				-	1104
	-	-	_	_	-						ttc Phe 380		_	-	•	1152
			_	_			-				gcc Ala		_	-	_	1200
-		-	_		-	-		-		Thr	cag Gln	-	-	-		1248
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267

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		260					265					270				
Leu Gli	n Arg 275		Arg	Leu	Leu	G1u 280	Val	Val	Thr	Ser	Ile 285	Ser	Asp	Пe		
Pro Thi		Ile	Pro	Val	His 295	Leu	Glu	Leu	Ala	Ser 300	Met	Thr	Asn	Arg		
Glu Lei		Ser	Ser	Ile 310		His	Gln	۷a٦	Phe 315		Ala	Val	Thr	Ser 320		
Leu Gly	/ Leu	Asn	G1u 325		Ġlu	Leu	Leu	Phe 330		Thr	Gln	Ser	A1a 335			
Gly Pro	His	Ser 340		Leu	Ser	Ser	Trp 345		Gly	Val	Pro	Asp 350		Gly		
Met Va	Ser 355		Пe	Leu	Phe	Trp 360		Leu	Lys	Glu	His 365		Arg	Ser		
Lys Ser 370	· Arg	Ala	Ser	Asp	Leu 375		Arg	Пe	His	Phe 380		Thr	Leu	Val		
Tyr His		Leu	Ala	Thr 390		Asp	Gly	His	Trp 395		Asn	Gln	Leu	A1a 400		
Ala Val	l Ala	Ala	Gly 405		Arg	Val	Ala	Gly 410		Gln	Ala	Cys	Ala 415			
Glu Thr	· Ile	Asp 420		Ser	Arg	۷al	Ser 425		Arg	Ala	Pro	G1n 430		Phe		
Met Thr	Ser 435		Ser	Glu	Ala	Gly 440		Arg	Пe	Val	Leu 445		Pro	Asn		
Lys Pro 450	Val	Val	Glu	Trp	His 455	Arg	Glu	Gly	Пe	Ser 460		His	Phe	Thr		
Pro Val 465	Leu	Val	Cys	Lys 470	Asp	Pro	Ile	Arg	Thr 475	Val	Gly	Leu	Gly	Asp 480		
Ala Ile	e Ser	Ala	G1u 485	Gly	Leu	Phe	Tyr	Ser 490	Glu	Val	His	Pro	His 495	Tyr		
<	:210> :211> :212> :213>	339 DNA	o sap	oiens	5											
<	:220> :221> :222>		(3	339)												
atg ggg Met Gly		cgg			_			-							4	8

269

											•	
	ggt Gly		-	-			-					96
	gcg Ala					-						144
_	tgt Cys 50	_										192
	tac. Tyr		_	-								240
	tgg Trp			-	_	-	-					288
	atc Ile	-	-	_	_	-				-	-	336
tga												339

<210> 190

<211> 112

<212> PRT

<213> Homo sapiens

<400> 190

Met Gly Ser Arg Leu Ser Gln Pro Phe Glu Ser Tyr Ile Thr Ala Pro 1 5 10 15

Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 20 25 30

Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 35 40 45

Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 50 55 60

Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser

65 Pro	Trp	Thr	He	Thr	70 Gln	Met	Val	Ile	Glv	75 Leu	Ser	Ile	Δla	Thr	80 Trn	
				85					90					95	·	
GIY	rie	Vai	100	Met	Ala	ASP	Pro	105		Lys	Ala	ıyr	Arg 110	Val	Val	
	<, <,	212>	630 DNA	o sar	oi en:	S										
	<;	220> 221> 222>		(6	530)											
>+ <i>~</i>		400>						+			~+~					40
				atg Met 5	_				_		_					48
				tgc Cys												96
				tgg Trp									-	_		144
				gga Gly							_	-				192
				gtt. Val												240
				aag Lys 85					_			-		_		288
				gcc Ala					-	-	_	_		_		336

271

			_				-		_		gcg Ala	_	384
				_	-				-	-	gac Asp		432
				_			 _	_		-	cga Arg	_	480
					_						att Ile 175	_	528
						_		-		-	acg Thr		576
											tgt Cys		624
ttg Leu	tga *												630

<210> 192

<211> 209

<212> PRT

<213> Homo sapiens

<400> 192

 Met Ala Ala Ala Ala Met Ala Ala Ser Ser Leu Thr Val Thr Leu Gly Arg

 1
 5
 10
 15

 Leu Ala Ser Ala Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly 20
 20
 25
 30

 Ala Ala Ser Leu Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln Ser Thr 35
 40
 45

 Ser Tyr Leu Pro Gly Tyr Val Pro Lys Thr Ser Leu Ser Ser Pro Pro 50
 55
 60

 Trp Pro Glu Val Val Leu Pro Asp Pro Val Glu Glu Thr Arg His His

65			•		70					75					80	
Ala	Glu	Val	Val	Lys 85	Lys	Val	Asn	Glu	Met 90	Пe	Val	Thr	Gly	G1n 95	Tyr	
			100			Val		105					110			
		115	·			Leu	120					125			_	
Gly	G1u 130	Arg	Ile	Arg	Leu	G1u 135	Lys	Val	Leu	Leu	Val 140	Gly	Ala	Asp	Asn	
145				-	150	Pro 、				155	·				160	
Glu	Ala	Thr	Val	Ile 165	Glu	Lys	Thr	Glu	Ser 170	Trp	Pro	Arg	I]e	Ile 175	Met	
Arg	Phe	Arg	Lys 180	Arg	Lys	Asn	Phe	L.ys 185	Lys	Lys	Arg	Пe	Val 190	Thr	Thr	
Pro	Gln	Thr 195	Val	Leu	Arg	Ile	Asn 200	Ser	Пe	Glu	Ile	A1a 205	Pro	Cys	Leu	
Leu																
	<2 <2 <2 <2 <2	220> 221>	351 DNA Homo	o sap	oiens 351)	5										
atg		100> tct		ttg	tcc	cag	cct	ttt	gag	tcc	tat	atc	act	gcg	cct	48
Met 1	Gly	Ser	Arg	Leu 5	Ser	Gln	Pro	Phe	Glu 10	Ser	Tyr	Ile	Thr	Ala 15	Pro	
			-	-		ccc Pro	_						-			96
		_				gca Ala	-		_	-	_	-		-		144
						999 Gly										192

273

50 55 60 gtg tac tgg gtg gca cgg aag ccc atg aag atg gga tac ccc ccg agt 240 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 65 70 75 cca tgg acc att acg cag atg gtc atc ggc ctc agt gag aat caa ggc 288 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 85 90 att gcc acc tgg ggt atc gtt gtc atg gca gac ccc aaa ggg aag gcc 336 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 tac cgc gtt gtt tga 351 Tyr Arg Val Val \* 115 <210> 194 <211> 116 <212> PRT <213> Homo sapiens <400> 194 Met Gly Ser Arg Leu Ser Gln Pro Phe Glu Ser Tyr Ile Thr Ala Pro 5 10 15 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 25 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 40 Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 55 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 70 75 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 90 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 110 Tyr Arg Val Val 115 <210> 195 <211> 1047

			DNA Homo	sa;	oiens	5										
	<2	220> 221> 222>		(	1047)	)										
atg	</td <td>100&gt; ctc</td> <td></td> <td>ggc</td> <td>tgg</td> <td>tgg</td> <td>caa</td> <td>gta</td> <td>ttg</td> <td>ctg</td> <td>tgg</td> <td>gtg</td> <td>ctg</td> <td>gga</td> <td>ctt</td> <td>48</td>	100> ctc		ggc	tgg	tgg	caa	gta	ttg	ctg	tgg	gtg	ctg	gga	ctt	48
	Arg															
	gtc Val	_				-	-		_	-		_				96
	gag Glu													-		144
	gag Glu 50					-	-						-	-	-	192
	gcc Ala				_									_		240
	ctg Leu												-			288
	agc Ser															336
	gtc Val															384
	gac Asp 130										-			-		432

_	_	-				gac Asp							_			480
						gag Glu										528
	-					atg Met		_			_	-		-		576
			-	-	-	act Thr		-	_				-		_	624
_			-	-	-	gcc Ala 215						_			_	672
		-				ttg Leu	-	_	-	-		-		-	_	720
						acc Thr	-	_	-							768
		-			_	gcc Ala	-					-	-		ctg Leu	816
-						att Ile									_	864
_				_		caa Gln 295	_	_							-	912
					-	gac Asp										960

276

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 tgg cta att cca gga caa gag cag gaa cat gtg gag tag 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu \* 340 345 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu 10 Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val 70 Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu 90 Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 135 140 130 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 150 155 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 205 200 Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala 215 Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

225					230					235					240	·	
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Va1 250	Pro	Asn	He	Leu	Leu 255	Phe		
Gln	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265	Asn	His	Thr	Asp ·	Arg 270	Thr	Leu		
Glu	Thr	Leu 275	Lys	Ile	Phe	Ile	Phe 280	Asn	Gln	Thr	Gly	Ile 285	Glu	Ala	Lys		
Lys	Asn 290	Val	Val	۷a٦	Thr	Gln 295	Ala	Asp	Gln		Gly 300	Pro	Leu	Pro	Ser		•
Thr 305	Leu	Ile	Lys	Ser	Val 310	Asp	Trp	Leu	Leu	Val 315	Phe	Ser	Leu	Phe	Phe 320	•	
Leu	Île	Ser	Phe	Ile 325	Met	Tyr	Ala	Thr	Ile 330	Arg	Thr	Glu	Ser	Ile 335	Arg		
Trp	Leu	Ile	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu						
	<'¿		444 DNA	o saņ	oiens	5											
	<2	220> 221> 222>		(4	144)							-					
_4_		100>					-11				_4_						40
						aaa Lys											48
-		-				gga Gly	-					_			-		96
						aaa Lys											144
					-	ggc Gly 55	_							_	_		192
						gtg Val									_		240

65					70					75					80	
				-	gga Gly	_	-	_	-	_			_	_	_	288
				-	gaa Glu								-		_	336
_	*			_	cca Pro				-		_					384
_	-		_	_	gcg Ala		-		_							432
	ctg Leu		tga *													444
	`<2	210>	100													
	<2 <2	211> 21 <b>2</b> >	147 PRT	o sap	oiens	5										
	<2 <2 <2	211> 212> 213> 400>	147 PRT Homo	·												
Met 1	<2 <2 <2	211> 212> 213> 400>	147 PRT Homo	·	oiens Lys		Leu	Gln	Gly 10	Leu	Val	Ala	Ala	Thr 15	Ile	
1	<2 <2 <2 Ala	211> 212> 213> 400> Phe	147 PRT Homo 198 Pro	Lys 5		Lys		Ile	10				Пe	15		
1 Thr	<2 <2 Ala Pro	211> 212> 213> 400> Phe Met	147 PRT Homo 198 Pro Thr 20	Lys 5 Glu	Lys	Lys Gly.	Glu Glu	I1e 25	10 Asn	Phe	Ser	Val Asn	Ile 30	15 Gly	Gln	
1 Thr Tyr	<2 <2 Ala Pro Val	211> 212> 213> 400> Phe Met Asp 35	147 PRT Homo 198 Pro Thr 20 Tyr	Lys 5 Glu Leu	Lys Asn	Lys Gly Lys Gly	Glu Glu 40	Ile 25 Gln	10 Asn Gly	Phe Val	Ser Lys Val	Val Asn 45	Ile 30 Ile	15 Gly Phe	Gln Val	
1 Thr Tyr Asn Gln	<2 <2 Ala Pro Val Gly 50	211> 212> 213> 400> Phe Met Asp 35 Thr	147 PRT Homo 198 Pro Thr 20 Tyr	Lys 5 Glu Leu Gly	Lys Asn Val Glu Trp	Lys Gly. Lys Gly 55	Glu Glu 40 Leu	Ile 25 Gln Ser	10 Asn Gly Leu	Phe Val Ser Lys	Ser Lys Val 60	Val Asn 45 Ser	Ile 30 Ile Glu	15 Gly Phe Arg	Gln Val Arg	
1 Thr Tyr Asn Gln 65	<2 Ala Pro Val Gly 50 Val	211> 212> 213> 400> Phe Met Asp 35 Thr	147 PRT Homo 198 Pro Thr 20 Tyr Thr Glu	Lys 5 Glu Leu Gly Glu Val	Lys Asn Val Glu	Lys Gly Lys Gly 55 Val	Glu Glu 40 Leu Thr	Ile 25 Gln Ser Lys	10 Asn Gly Leu Gly Leu	Phe Val Ser Lys 75	Ser Lys Val 60 Asp	Val Asn 45 Ser Lys	Ile 30 Ile Glu Leu	15 Gly Phe Arg Asp Glu	Gln Val Arg Gln 80	
1 Thr Tyr Asn Gln 65 Val	<2 Ala Pro Val Gly 50 Val Ile	211> 212> 213> 400> Phe Met Asp 35 Thr	147 PRT Homo 198 Pro Thr 20 Tyr Thr Glu His	Lys 5 Glu Leu Gly Glu Val 85	Lys Asn Val Glu Trp 70	Lys Gly Lys Gly 55 Val	Glu Glu 40 Leu Thr	Ile 25 Gln Ser Lys Ser	10 Asn Gly Leu Gly Leu 90	Phe Val Ser Lys 75 Lys	Ser Lys Val 60 Asp Glu	Val Asn 45 Ser Lys Ser	Ile 30 Ile Glu Leu Gln	15 Gly Phe Arg Asp Glu 95	Gln Val Arg Gln 80 Leu	

		115					120					125				
Lys	Glu 130		Ala	Ala	Ala	Pro .135		Pro	Cys	His	Phe 140		Thr	Ile	Thr	
Phe 145	Leu	Pro														
		210>														
		211> 212>														
				s ap	oiens	5									. •	
•		220> 221>	cns													
			(1).	(7	705)										-	
				_	ature											
			(1). n =		, C o	^ G							•			
2+0		100>		~~+	201			++-	+-+	+02	20+	+++	~~~	+-+	200	40
Met	-			Gly	_	cag G]n		-	Tyr				-	Tyr		48
1				5					10					15		
	_	-	-		-	gag Glu	_	_			_			_	_	96
			20					25					30		,	
	_	-				cat	-		-						-	144
ıyı	net	35	Lys	rie	rne	His	40	Leu	Asp	nec	Leu	45	1111	Vai	um	
						att										192
Glu	50	Asn	Glu	Pro	Val	Ile 55	iyr	Asn	Arg	Ala	Arg 60	Phe	iyr	Val	lyr	
						gtc										240
Asn 65	Lys	Lys	Lys	Arg	Leu 70	Val	Asn	Thr	Pro	Tyr.	Val	Asp	Asn	Ser	Tyr 80	
	too	act	aat	aat		+++	cta	+o+	202		aat	a 2 C	ctt	cta		288
		-		Gly		ttt Phe	_		Thr					Leu		200
				85					90					95		

			tat Tyr							336
			cct Pro							. 384
			cct Pro 135			-		-		432
			tgg Trp							480
			cgg Arg							528
			ctg Leu							576
			gtt Val							624
			gtt Val 215							672
	-	_	gac Asp	-	_	tga *				705

<210> 200

<211> 234

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(234) <223> Xaa = Any Amino Acid

<400> 200

Met Met Ser Gln Gly Ser Gln Phe Leu Tyr Ser Thr Phe Gly Tyr Thr 10 Leu Leu Ala Ala Ile Val Glu Arg Ala Ser Gly Cys Lys Tyr Leu Asp Tyr Met Gln Lys Ile Phe His Asp Leu Asp Met Leu Thr Thr Val Gln Glu Glu Asn Glu Pro Val Ile Tyr Asn Arg Ala Arg Phe Tyr Val Tyr 55 Asn Lys Lys Lys Arg Leu Val Asn Thr Pro Tyr Val Asp Asn Ser Tyr 70 75 Lys Trp Ala Gly Gly Gly Phe Leu Ser Thr Val Gly Asp Leu Leu Lys 90 Phe Gly Asn Ala Met Leu Tyr Gly Tyr Gln Val Gly Leu Phe Lys Asn 105 Ser Asn Glu Asn Leu Leu Pro Gly Tyr Leu Lys Pro Glu Thr Met Val 120 Met Met Trp Thr Pro Val Pro Asn Thr Glu Met Ser Trp Asp Lys Glu Gly Lys Tyr Ala Met Ala Trp Gly Val Val Glu Xaa Lys Gln Thr Tyr -150 155 Gly Ser Cys Arg Lys Gln Arg His Tyr Ala Ser His Thr Gly Gly Ala 170 Val Gly Ala Ser Ser Val Leu Leu Val Leu Pro Glu Glu Leu Asp Thr 185 Glu Thr Ile Asn Asn Lys Val Pro Pro Arg Gly Ile Ile Val Ser Ile 200 Ile Cys Asn Met Gln Ser Val Gly Leu Asn Ser Thr Ala Leu Lys Ile 215 220 Ala Leu Glu Phe Asp Lys Asp Arg Ser Asp 225 230

<210> 201

<211> 885

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(885)

282

<221> misc\_feature <222> (1)...(885) <223> n = A.T.C or (

<223> n = A.T.C or G<400> 201 atg ctg gct gtg tca gtg ctg gcc gca gtc cgc ggc ggc gac gag gtg 48 Met Leu Ala Val Ser Val Leu Ala Ala Val Arg Gly Gly Asp Glu Val 1 5 10 15 agg cgc gtc cgc gag agc aac gtc ctc cac gag aag tcc aag ggg aag 96 Arg Arg Val Arg Glu Ser Asn Val Leu His Glu Lys Ser Lys Gly Lys 20 25 acg cgc gag gga gcc gag gac aag atg acc agc ggc gac gtg ctg tcc 144 Thr Arg Glu Gly Ala Glu Asp Lys Met Thr Ser Gly Asp Val Leu Ser 35 40 aac cgc aag atg ttc tac ctg ctc aag acc gcc ttc ccc agc qtc cag 192 Asn Arg Lys Met Phe Tyr Leu Leu Lys Thr Ala Phe Pro Ser Val Gln 50 55 60 att aat act gag gaa cac gtg gat gca gct gat cag gag gtt atc ttg 240 Ile Asn Thr Glu Glu His Val Asp Ala Ala Asp Gln Glu Val Ile Leu 65 70 tgg gat cat aag att cct gag gat atc cta aag gaa gta act act cct 288 Trp Asp His Lys Ile Pro Glu Asp Ile Leu Lys Glu Val Thr Thr Pro 85 95 aaa gag gta cca gca gaa agt gtt act gtc tgg att gac cca ctt gat 336 Lys Glu Val Pro Ala Glu Ser Val Thr Val Trp Ile Asp Pro Leu Asp 100 105 gct aca cag gaa tat aca gag gat ctt cga aag tac gtc act act atg 384 Ala Thr Gln Glu Tyr Thr Glu Asp Leu Arg Lys Tyr Val Thr Thr Met 115 120 125 gtg tgt gtg gct gta aat ggt aaa ccc atg cta gga gtt ata cat aag 432 Val Cys Val Ala Val Asn Gly Lys Pro Met Leu Gly Val Ile His Lys 130 135 140 cca ttt tcc gaa tat aca gct tgg gca atg gta gat ggt ggt tca aat 480 Pro Phe Ser Glu Tyr Thr Ala Trp Ala Met Val Asp Gly Gly Ser Asn 145 150 155 160

	-	-		tcc Ser				_					•			528
-				999 Gly	_	-		-	-	-		_				576
	_			att Ile			_			-				_		624
				gtg Val		-				-		-	_			672
				tac Tyr 230			-		-		-	_				720
			-	cta Leu				_			_	_		•		768
				ggt Gly		-			_					_	,	816
				cac His												864
aag Lys 290				aaa Lys	tga *											885

<210> 202

<211> 294

<212> PRT

<213> Homo sapiens

<220>

284

<221> VARIANT

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	<2 <2	210> 211> 212> 213>	861	o saj	oi en:	<b>S</b> -										
	<2	220> 221> 222>	CDS (1)	(8	361)											
-	qag Glu	-	aaa	-		_	_	-	-			-		-	_	48
	gtt Val		-	_	_		_	_		_			-	_	_	96
	ctc Leu			-												144
	tct Ser 50					_						-	-	_	_	192
_	gct Ala				-			-	_					_		240
-	ctg Leu					-										288
-	gac Asp			-	-	_			-	-			-		-	336
_	ccc Pro			_					-		-				_	384
	cca Pro	-			-				_							432

286

	130					135					140					
-			_	-	cca Pro 150								_	_		480
	_		-		gaa Glu											528
					cgc Arg			_	-	_		-			-	576
-	-	-			cta Leu			_				-			_	624
		-		•	aca Thr			_	_	_	_				_	672
			_		aca Thr 230			-	_		-			_	-	720
			_		atc Ile	-	-					_	-		-	768
	_				gaa Glu				-	-	-	_			Ψ.	816
				_	tat Tyr		_		_		-			tga *		861

<210> 204

<211> 286

<212> PRT

<213> Homo sapiens

	<	400>	204												
Met 1	Glu	Glu	Lys	Arg 5	Arg	Arg	Ala	Arg	Val 10	Gln	Gly	Ala	Trp	Ala 15	Ala
		Lys	20					25					30	_	
His	Leu	His 35	Gln	Lys	Pro	Gly	G1n 40	Thr	Trp	Lys	Asn	Lys 45	Glu	His	His
	50	Asp	•			55		•			60				
Arg 65	Ala	Pro	Glu	Pro	Arg 70	Val	Ile	Asp	Arg	G1u 75	Gly	Val	Tyr	Glu	Ile 80
Ser	Leu	Ser	Pro	Thr 85	Gly	Val	Ser	Arg	Va1 90	Cys	Leu	Tyr	Pro	G1y 95	Phe
		Val	100					105					110		
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	-	Asn	180	•	·			185	·			·	190		
		G1u 195					200					205			
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225		Gly			230					235					240
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<212> DNA

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cat gca tca ttg gat tta tcc tcc cca tgt ttc ctg tct gta gga tct 480

155

His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser

150

105

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	-		_		gct Ala	-	-				-	-					624
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Cys	G1u 50	Ile	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	Glu 60	Glu	Leu	Thr	Ser
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Ala	Пe	Trp 275		Gly	Val	Tyr		Gly	-	Tyr	Leu	Thr 285	Phe	Leu	Thr
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His 305	Tyr	Phe	Пе	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	Ile 320
Thr	Trp	Пe	Val	Thr 325	Gln	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
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297

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Lys 385	Thr	Ala	Thr	Ala	Leu <sub>.</sub> 390	Leu	Glu	Ser	Pro	Leu 395	Ser	Ala	Thr	Val	G1u 400	•
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	Lys		420					425		-			430		•	
Lys	Asn	.Ser 435	G]u	Ala	Arg	Trp	Trp 440	Met	Lys	Leu	Ala	Leu 445	Glu	Leu	Pro	
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	Asp															40

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					ctc Leu					•					_	144
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_				_	99c Gly 70	_	-	_				-	-	_	_	240
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_		-		_	ttt Phe	_	-			-			•	_		336
	_				tcc Ser	_	-	_	_	-			_	_		384
_					tgg Trp	-						-	-		_	432
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				_	gag Glu	-	-		-		-	_	_		_	576

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-	 -				_				_	-	_		gtt Val 255		768
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301

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PCT/US00/29052

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	-			_	_	-							agc Ser 110			336
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											_		acg Thr			432
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	ggc Gly			tga *												495
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Gln	Ala	A1 a 35		Trp	Gln	Phe	G1u 40		Ala	Leu	Ser	Thr 45	Phe	Phe	Gln	
Glu	Thr 50	Asn	Ile	Pro	Asn	Ser 55	His	His	His	His	G1n 60	Met	Met	Cys	Thr	
Pro 65	Ser	Asn	Thr	Pro	A1a 70	Thr	Pro	Pro	Asn	Phe 75	Pro	Asp	Ala	Leu	Ala 80	

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			Glu	caa Gln												384
				gaa Glu												432
				aag Lys												480
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					-	-							gag Glu		-	960
-	-	-	-		-		-	-			-		gaa Glu	_	-	1008
													caa G1n 350			1056
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PCT/US00/29052

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140

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314 -

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	tgc Cys															96
	gac Asp	-	_			-		_	_						_	144
	acc Thr 50															192
	cca Pro															240
	atg Met		-		_		_	_					-			288
	tta Leu															336
cgg	ctg	ctg	gca	cag	999	tga				•		•				357

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Ile Cys Leu Phe Val Asp Ile Leu Pro Val Glu Thr Val Leu Arg Ile
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Trp Asp Cys Leu Phe Asn Glu Gly Ser Lys Ile Ile Phe Arg Val Ala
Leu Thr Leu Ile Lys Gln His Gln Glu Leu Ile Leu Glu Ala Thr Ser
Val Pro Asp Ile Cys Asp Lys Phe Lys Gln Ile Thr Lys Gly Ser Phe
Val Met Glu Cys His Thr Phe Met Gln Lys Ile Phe Ser Glu Pro Gly
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tgg gcc tcc gtg agc gcc cag acc gat gcc acc ccg gcg gtg acg aca
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Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
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                                 25
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									gct Ala						192
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									tgc Cys						288
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			-					_	gta Val		-		_	-	432
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_						_	-		gat Asp	-				•	528
									ttg Leu		-	-			576
					Leu				act Thr						624

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												ttt Phe		720
				-	-						-	cag Gln 255	-	768
												gaa Glu		816
	-		-		-			_			Val	cag Gln		864
_		_					-		-			gac Asp		912
	_	-	-			-		_			_	ctt Leu	•	960
	_	-			-	_		_				gat Asp 335	_	1008
												gtt Val		1056
												ctt Leu		1104
							-					gtc Val		1152

	tta gct gct Leu Ala Ala 390					1200
att cag acc Ile Gln Thr	aca aat aga Thr Asn Arg 405	tat gga cag Tyr Gly Gln	ctt act at Leu Thr Il 410	ct ctt cat le Leu His	agc aca Ser Thr 415	1248
act gag caa Thr Glu Gln	gạc tgc tta Asp Cys Leu 420	gca ctg gag Ala Leu Glu 425	ggg gtc cg Gly Val Ar	gg acc cca rg Thr Pro 430	gta tta Val Leu	1296
	act atg caa Thr Met Gln					1344
	cag ctc gta Gln Leu Val			er Leu Leu		1392
cag ggc ttc Gln Gly Phe 465	cca gat tac Pro Asp Tyr 470	Val Ala Pro	ttt gga aa Phe Gly As 475	at tcc cag sn Ser Gln	gcc cag Ala Gln 480	1440
gac atg ctg Asp Met Leu	gac tgg gtg Asp Trp Val 485	ccc atc cac Pro Ile His	ttc atc ac Phe Ile Th 490	cc cag tca nr Gln Ser	ttc aac Phe Asn 495	1488
	tcc tgc cag Ser Cys Gln 500		Ala Leu Va			1536
	tac gga tcc Tyr Gly Ser					1584
	aat cta att Asn Leu Ile		Phe Pro G1			1632
	acg att ctt Thr Ile Leu 550	lle Ser Thr				1680

1728 tot goa cot goa gag goa ggo tto aga got coa coa goo ato aat goo Ser Ala Pro Ala Glu Ala Gly Phe Arg Ala Pro Pro Ala Ile Asn Ala 570 565 1764 agg ctg ccc ttt aac ttc ttc ttc ccg ttt gtt tga Arg Leu Pro Phe Asn Phe Phe Phe Pro Phe Val \* 585 580 <210> 226 <211> 587 <212> PRT <213> Homo sapiens <400> 226 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys 10 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr 25 Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser 55 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp 90 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val 105 100 Val Thr Gly Asp Ser Gln Phe Cys Ser Gln Lys Ala Val Ile Tyr Ser 120 Leu Asn Phe Thr Ala Asn Pro Pro Gln Arg Val Phe Glu Leu Val Asp 135 Gln Ile Asn Pro Ser Ile Phe Cys Ile His Ile Thr Asn Tyr Lys Pro 145 150 155 160 Ala Leu Ser Phe Ile Asn Pro Glu Val Pro Asp Glu Asn Asn Phe Asp 170 Thr Leu Met Lys Thr Ser Asp Gly Phe Thr Leu Asn Ala Glu Ser Tyr 185 Val Ser Phe Thr Thr Lys Leu Asp Ile Pro Thr Ala Ala Lys Tyr Glu 200 Tyr Gly Val Pro Leu Gln Thr Ser Asp Ser Phe Leu Arg Phe Pro Ser 215 220 210

Ser	Leu	Thr	Ser	Ser	Leu	Cys	Thr	Asp	Asn		Pro	Ala	Ala	Phe	Leu
225					230					235					240
۷al	Asn	Gln	Ala	Val	Lys	Cys	Thr	Arg	Lys	Ile	Asn	Leu	Glu	Gln	Cys
				245					250		_	_	_	255	
Glu	Glu	Пe	Glu	Ala	Leu	Ser	Met		Phe	lyr	Ser	Ser		Glu	He
		_	260					265				~.	270	03	•
Leu	Arg		Pro	Asp	Ser	Arg		Lys	Val	Pro	He		Val	Gin	Ser
	_	275		_			280			~~1		285	0.7		
He		He	Gln	Ser	Leu		Lys	ihr	Leu	Inr		Arg	Glu	Asp	ınr
	290					295		<b>A</b>	۸٦	01	300	Dh.a	C	1	Cur
		Leu	Gln	Pro		Leu	vai	Asn	Ala			Pne	Ser	Leu	
305			W-7		310	V-3	1	Т	C 0.2	315		Tun	Thn	۸۵۵	320
vai	Asn	vai	Val		GIU	vai	Lys	ıyr		Leu	1111.	1 yr	HIII.	335	Ala
01	<b>61</b>	W-7	Tl	325	۸٦	۸	1 0	Con	330	Val	Lou	Clv	Thn		San
ыу	GIU	vai	Thr	Lys	Ald	ASP	Leu	345	rne	vai	Leu	uiy	350	vai	3 <del>C</del> 1
Can	V-7	V-3	340 Val	Dno	1 011	Cln	Cln		Dho	GTu	Πa	Hic		ا م	Gln
26L	VdI	355	Vdi	Pro	Leu	GIII	360	Lys	rne	uiu	116	365	THE	Leu	um
Clu	Acri		Gln	Dro	Val	Dro		Sar	Glv	Δsn	Pro		Tvr	Val	Val
Giu	370	1111	um	FIU	vai	375		JCI	اوانا	7.511	380	415	',		,
Glv		Pro	Leu	Δla	Αla			Gln	Pro	His		Glv	Ser	Glv	Пe
385		,10	LCU	/ \	390	u,j		<b>G</b>		395		5			400
		Thr	Thr	Asn		Tvr	G1 y	Gln	Leu			Leu	His	Ser	Thr
1.0	٠			405		, ,			410					415	
Thr	Glu	Gln	Asp			Ala	Leu	Glu	Gly	Val	Arg	Thr	Pro	۷a٦	Leu
			420	٠				425	•				430		
Phe	Gly	Tyr	Thr	Met	Gln	Ser	Gly	Cys	Lys	Leu	Arg	Leu	Thr	Gly	Ala
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Leu	Pro	Cys	Gln	Leu	Val	Ala	Gln	Lys	Val	Lys	Ser	Leu	Leu	Trp	Gly
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Gln	Gly	Phe	Pro	Asp	Tyr	Val	Ala	Pro	Phe		Asn	Ser	Gln	Ala	Gln
465					470					475					480
Asp	Met	Leu	Asp	Trp	۷a۱	Pro	Пe	His			Thr	Gln	Ser	Phe	Asn
				485					490					495	
Arg	Lys	Asp	Ser	Cys	Gln	Leu	Pro			Leu	Val	He		Val	Lys
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Trp	Thr	Lys	Tyr	Gly	Ser	Leu			Pro	Gln	Ala			Val	Asn
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Val			Asn	Leu	He			Ser	Phe	Pro		Ala	Asn	Ser	Gly
	530					535					540	D'			
		Arg	Thr	He			Ser	Thr	Ala			Phe	Val	Asp	Val
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Ser	Ala	Pro	Ala			Gly	Phe	Arg			Pro	Ala	Пе		Ala
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			agt cta gca ggc Ser Leu Ala Gly 60	
		-	tgg gtc acc gtt Trp Val Thr Val 75	
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			gca tcg gcc gtg Ala Ser Ala Val	
	Leu Ala Ser		ctc tgc cgc tac Leu Cys Arg Tyr 125	

												gcc Ala				432
												cac His				480
												tcc Ser				528
												999 G1y				576
												ctc Leu 205				624
												tat Tyr				672
												gtg Val				720
												gtg Val				768
gtg Val	gtg Val	gtg Val	gtc Val 260	ttg Leu	ctg Leu	ctg Leu	cag Gln	999 Gly 265	ctg Leu	tcc Ser	ctg Leu	ctc Leu	gag Glu 270	ctg Leu	ctt Leu	816
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												ttt Phe				912

Asp 305	agc Ser															960 963	
tga *																	
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Leu	Ala		20	Ser				25					30	Asp			
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Phe	Arg 50		Arg	Gln	Pro	Ile 55	Tyr	Met	Ser	Leu	A1a 60	Gly	Trp	Thr	Cys		
Arg 65	Asp	Asp	Cys	Lys	Tyr 70	Glu	Cys	Met	Trp	Val 75	Thr	Val	Gly	Leu	Tyr 80		
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Ser	Arg	Phe	Leu 100		Phe	Gln	Glu	Pro 105	Ala	Ser	Ala	Val	Ala 110	Ser	Phe		
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Val 145	Ser	Leu	Aśn	Ala	Trp 150				Thr	Val 155	Phe	His	Thr	Arg	Asp 160		
	Asp	Leu	Thr	G1u 165		Meţ	Asp	Tyr	Phe 170	Cys	Ala	Ser	Thr	Val 175	Ile		
Leu	His	Ser	Ile 180		Leu	Cys	Cys	Val 185		Thr	Val	Gly	Leu 190		His		
Pro	Ala	Val 195		Ser	Ala	Phe	Arg 200		Leu	Leu	Leu	Leu 205		Leu	Thr		
Val	His 210		Ser	Tyr	Leu	Ser 215		Ile	Arg	Phe	Asp 220		Gly	Tyr	Asn		

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	Trp	Cys	Leu	Trp 245	Asn	Gln	Arg	Arg	Leu 250		His	Val	Arg	Lys 255		
Val	Val	Val	Val 260	Leu	Leu	Leu	Gln	Gly 265	Leu	Ser	Leu	Leu	G1u 270	Leu	Leu-	
Asp	Phe	Pro 275	Pro	Leu	Phe	Trp	Val 280	Leu	Asp	Ala	His	A1a 285	Ile	Trp	His	
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Asp 305	Şer	Leu	Tyr	Leu	Leu 310	Lys	Glu	Ser	Glu	Asp 315	Lys	Phe	Lys	Leu	Asp 320	
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Met 1 cgc		222> 223> 400> cgg Arg	(1) n = 229 aag Lys	aag Lys 5	557) ,C or gtg	cgt Arg	Pro caa	Arg ctg	Leu 10 aac	Ile agg	Ala ccg	Xaa cgc	Leu gac	Ala 15 tcc	Arg cag	48 96
Met 1 cgc Arg	<pre>&lt;2 gcg Ala gtg Val tac</pre>	222> 223> 400> cgg Arg cgc Arg	(1) n = 229 aag Lys gcc Ala 20 gtg	aag Lys 5 ctg Leu	557) C or gtg Val	cgt Arg gag Glu	Pro caa Gln acc	ctg Leu 25	Leu 10 aac Asn	Ile agg Arg	Ala ccg Pro	Xaa cgc Arg	gac Asp 30	Ala 15 tcc Ser	Arg cag Gln cgc	
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.334

Leu 65	Gln	Leu	Leu	Gly	Arg 70	Leu	Pro	Leu	Phe	Gly 75	Leu	Gly	Arg	Leu	Va1 80	
_	-	_			-						-	-		tgg Trp 95	_	288
	_					_		-	-	-		-	-	caç His		336
			ĠΊy											gag Glu		384
			_		_	_			_			_		ccc Pro	-	432
				-					-	-		-	_	gac Asp	_	480
_	_			_		_					-	_		atc Ile 175	_	528
_	_	_				_		-		-			_	ctg Leu		576
	~			•	_	-			_			_		cag Gln	-	624
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Arg Leu Pro Val Arg Ala Trp Ala Asp Val Arg Arg Glu Xaa Arg Leu
Leu Gln Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
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                                        75
Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
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Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
                            120
                                                125
Arg Glu Ile Glu His Val Met Tyr His Asp Trp Arg Leu Val Pro Lys
                        135
                                            140
His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
                    150
                                        155
Leu Ala Ser Val Pro Tyr Pro Pro Leu Leu Arg Ala Met Ile Ile Ala
                                    170
Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
                               185
Val Gln Arg Ile Arg Met Glu Pro Trp Asp Tyr Pro Ala Lys Gln Glu
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Asp Lys Gly Arg Ala Lys Gly Thr Pro Val
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336

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			tgg gcc ctg gtg Trp Ala Leu Val	
	7 Thr Cys Pro		ctg gtg att ggc Leu Val Ile Gly 205	Ser Arg Leu
			cgg cta gcc ttc Arg Leu Ala Phe 220	
			tac gcc gac agc Tyr Ala Asp Ser 235	_
			aag cat ggc ctt Lys His Gly Leu 250	
	·		cgc tcc ctg ttc Arg Ser Leu Phe	
	e Gln Leu Phe	Val Gly Leu	aag gtg cac ttg Lys Val His Leu 285	Ser Thr Gly
			ggc cag agc ggc Gly Gln Ser Gly 300	
		_	gag tcc aag aag Glu Ser Lys Lys 315	
			ggc cgt ggg gag Gly Arg Gly Glu	

338

325 330 335 cag gag gag agc gcc gag cgg agn agg ccc tca cag cat gtg gtg ctc 1056 Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu 340 345 ago ctg act ttc aag cgt tat gtc ttc gac acc cac aag cgc atg gtt 1104 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 360 365 cag tct ccc tga 1116 Gln Ser Pro \* 370 <210> 232 <211> 371 <212> PRT <213> Homo sapiens <220> <221> VARIANT · <222> (1)...(371) <223> Xaa = Any Amino Acid <400> 232 Met Ser Val Ala His Cys Phe Ser Ile Lys Gly Gln Gly Thr Val Met 10 Thr Gly Thr Ile Leu Ser Gly Ser Ile Ser Leu Gly Asp Ser Val Glu 25 Ile Pro Ala Leu Lys Val Val Lys Lys Val Lys Ser Met Gln Met Phe 40 His Met Pro Ile Thr Ser Ala Met Gln Gly Asp Arg Leu Gly Ile Cys 55 Val Thr Gln Phe Asp Pro Lys Leu Leu Glu Arg Gly Leu Val Cys Ala 70 75 Pro Glu Ser Leu His Thr Val His Ala Ala Leu Ile Ser Val Glu Lys Ile Pro Tyr Phe Arg Gly Pro Leu Gln Thr Lys Ala Lys Phe His Ile 105 Thr Val Gly His Glu Thr Val Met Gly Arg Leu Met Phe Phe Ser Pro 120 125 Ala Pro Asp Asn Phe Asp Gln Glu Pro Ile Leu Asp Ser Phe Asn Phe 130 135 140

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Ser Gln Glu Tyr Leu Phe Gln Glu Gln Tyr Leu Ser Lys Asp Leu Thr
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Pro Ala Val Thr Asp Asn Asp Glu Ala Asp Lys Lys Ala Gly Gln Ala
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Thr Glu Gly His Cys Pro Arg Gln Gln Trp Ala Leu Val Glu Phe Glu
                                185
Lys Pro Val Thr Cys Pro Arg Leu Cys Leu Val Ile Gly Ser Arg Leu
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Asp Ala Asp Ile His Thr Asn Thr Cys Arg Leu Ala Phe His Gly Ile
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                                            220
Leu Leu His Gly Leu Glu Asp Arg Asn Tyr Ala Asp Ser Phe Leu Pro
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                                        235
Arg Leu Lys Val Tyr Lys Leu Lys His Lys His Gly Leu Val Glu Arg
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                                    250
Ala Met Asp Asp Tyr Ser Val Ile Gly Arg Ser Leu Phe Lys Lys Glu
                                265
Thr Asn Ile Gln Leu Phe Val Gly Leu Lys Val His Leu Ser Thr Gly
                            280
                                                285
Glu Leu Gly Ile Ile Asp Ser Ala Phe Gly Gln Ser Gly Lys Phe Lys
                        295
                                            300
Ile His Ile Pro Gly Gly Leu Ser Pro Glu Ser Lys Lys Ile Leu Thr
305
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                                        315
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Pro Ala Leu Lys Lys Arg Ala Arg Ala Gly Arg Gly Glu Ala Thr Arg
                                    330
                325
Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu
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Gln Ser Pro
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		-	_	-	-								gtg Val		144
													gta Val		192
				-		_	_				 		gcc Ala	_	240
		-						-					tca Ser 95		288
_			-			_	_	-				-	cat His		336
_		_	_		_			-					cag G1n		384
		-											ga't Asp		432
-	_							-					aaa Lys		480
•		-		-				-	-				gta Val 175		528

tct Ser		-						-	-		aaa Lys	-	_			576
gaa Glu				-			-									624
Пe		Ser									ttg Leu 220					672
	_	•		_			_				tat Tyr		-			720
-					-						att Ile		-			768
	_			~~						_	gat Asp	Ile	•	•	•	816
gaa Glu					-		-			-	ttc Phe			-		864
Arg			-	-					-	_	atc Ile 300			_		912
aca Thr 305											cgt Arg					960
tca Ser																1008
act Thr			_		_	_				_	att Ile				-	1056

	cct Pro															1104
	gct Ala 370															1152
	cct Pro															1200
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Gly	Pro	Arg 35		Ser	۷a٦	Thr	Asn 40		Ser	Gly	Pro	Arg 45		Val	Ser	
Ile	A1a 50		Thr	Arg	Pro	Ser 55		Arg	Asn	Gly	G]n 60	-	Leu	Val	Ser	
Thr 65	Gly	Leu	Pro	Ala	Leu 70		Gln	Leu	Leu	Gly 75		Gly	Leu		Va1 80	
	Thr	Val	Leu	Leu		Glu	Glu	Asp	Lys		Asn	Ile	Tyr			

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Leu	Pro 130		Pro	Leu	Leu	Asp 135		Lys	Cys	Lys	Lys 140	Glu	Phe	Asp	Glu
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	Trp	Arg	Tyr	G1n 165		Leu	Pro	Lys	Met 170		Ile	Gly	Pro	Val 175	
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Glu	Leu	Ile 195	Glu	Ala	Ser	Asn	Trp 200	His	Gly	Phe	Phe	Leu 205	Pro	Glu	Lys
Пe	Ser 210	Ser	Thr	Leu	Lys	Val 215	Glu	Pro	Cys	Ser	Leu 220	Thr	Pro	Gly	Tyr
Thr 225	Lys	Leu	Leu	Gln	Phe 230	Пe	Gln	Asn	Пe	Ile 235	Tyr	Glu	Glu	Gly	Phe 240
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		355					360		,			Asp 365		-	•
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Leu 385	Pro	Pro	Asp	Leu	Ser 390	Asp	Thr	Val	Ser	Arg 395	Ser	Ser	Lys	Met	Asp 400
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-		-			cag Gln	-									432

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_					_	_					gag Glu			528
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											ctg Leu 205			624
			_							 -	ctg Leu	_	 _	672
	-	_	-	Leu		_		_			aca Thr	-	 	720
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	-					-					atc Ile		 -	816
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	-					-					cca Pro			960

346

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Met	He	Gln	Glu	Пe	Gln	Gln	Ala	Ala		Arg	Leu	Glu	Arg		Phe
				165				_	170		_			175	_
Val	Asp	Ser	-	Gln	Leu	Lys	Val		Ala	Thr	Çys		Asp	Leu	Ser
	<b>C</b> .		180	<b>A</b>	W-7	1	61	185	The se	T 7 _	These		190	D	C1
vaı				_	vai	Leu	200	met	ınr	116	Inr	205	۷a٦	Pro	GIU
110	Dho	195		Tnn	Thn	۸۵۵		Thr	Sor	67	Mat		Leu	۸na	۸۳۵
TIE	210	Leu	ASP	пр	-1()(	215	FIU		361	uiu	220	Leu	Leu	Ai 9	AI Y
l eu		Gln	Leu	Геп	Asn		Val	Leu	Asn	Ara		Thr	Ala	Glu	Ara
225	/ \	u III	LCu	LCu	230		• • •		, 1511	235	• • •	••••	,,,,	a.u	240
	Leu	Phe	Asp	Arg					Arg		Pro	Gly	Leu	Glu	
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Val	Asp	His	Tyr	Pro	Пe	Leu	Val	Ala	Val	Thr	Gly	Пe	Leu	۷a٦	Gln
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Leu		Ala	Asp	Pro	Cys		Gln	Leu	Arg	Ser		Cys	Tyr	Leu	Leu
01	290	D	01	D	Dista	295	D	C1	Tha	47.	300	Dan	۸٦.	Daa	۸ ۵ ۵
•	Gin	Pro	GIU	Pro		АГа	Pro	ыу	Inr	315	Leu	Pro	Ala	Pro	320
305	Lvc	۸ra	Dha	Sar	310	Gln	Sar	Tvr	Δla		Tvr	م ۱۱	Ser	Δla	
Aig	Lys	Ai y	THE	325	LCU	um	301	1 91	330	ДЗР	יעי	110	JC1	335	Λ3þ
Glu	Leu	Ala	Gln		Glu	Gln	Met	Leu		His	Leu	Thr	Ser	,	Ser
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Ala	Gln	Ala	Ala	Ala	Ala	Ser	Leu	Pro	Thr	Ser	Glu	Glu	Asp	Ser	Ala
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Pro	Ser	Ala	Met	Pro	Thr	Pro	Ser	Leu	Leu	Cys	Ser	Ser	Pro	۷a٦	Ala
	370					375					380				
	Ser	Pro	Ala	Lys		۷al	Ser	Thr	Ser						
385					390					395					
		210	007												
		210>		,											
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			Homo	n car	niano	-									
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	-			t aca gct tta u Thr Ala Leu 45	_
-				c atg cag ata n Met Gln Ile O	_
-	-	Gln Leu Le		a gaa ttt tcc 1 Glu Phe Ser	_
		-		c att gca aat s Ile Ala Asn 95	-
	_	_	a Pro Ala Glu	a tgg gta gcc u Trp Val Ala 110	-
	•			a gtt gtg gat 1 Val Val Asp 125	
		_		t gag aaa gtg n Glu Lys Val O	
				t ttg aag tat r Leu Lys Tyr	

145	•				150					155					160	
														ctc Leu 175	-	528
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		_	_	_			_							gat Asp		624
				_				-						gag Glu		672
	-		_			-	_		_					agc Seŗ		720
					_					_	_		-	ggt Gly 255		768
	_		_			_						-		tct Ser		816
		_	-			_		-	_	_		_		tct Ser		864
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_				-	-			-				_	_	aga Arg		1008

350

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45

40

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Lys	Arg	Ser	Gln	Asp 325	Val	Leu	His	Arg	Tyr 330	He	Glu	Asp	Glu	Arg 335	Leu
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WO 01/29221

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					caa Gln 150											480
					tct Ser											528
					att Ile											576
					ctt Leu											624
					gag Glu							Thr				672
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					cta Leu											768
					gag G1u											816
					gtt Val						Ala					864
aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	caa	gga	912

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Ser Pro Glu Tyr 65	Phe Pro Val 50	Ala His 35 Met	Glu 20 Thr Glu Pro	5 Ser Val Glu Ile Leu	Trp Asn Val Phe 70	Asp Thr Leu 55 Arg	Asn Leu 40 Gln Pro	Val 25 Phe Lys Met	10 Gly Leu Lys Lys	Leu Thr Ala Arg 75	Leu Asn Asp 60 Ile	Val Asp 45 Leu Thr	Glu 30 Leu Ile Trp	15 Pro Thr Leu Asn Gly	Ser Glu Ser Thr	
Ser Pro Glu Tyr 65 Trp	Phe Pro Val 50 His	Ala His 35 Met Pro Glu	Glu 20 Thr Glu Pro Arg	5 Ser Val Glu Ile Leu 85	Trp Asn Val Phe 70 Val	Asp Thr Leu 55 Arg	Asn Leu 40 Gln Pro Arg	Val 25 Phe Lys Met Ala	10 Gly Leu Lys Lys Leu 90	Leu Thr Ala Arg 75 Glu	Leu Asn Asp 60 Ile Asn	Val Asp 45 Leu Thr	Glu 30 Leu Ile Trp Val	15 Pro Thr Leu Asn Gly 95	Ser Glu Ser Thr 80 Ile	
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	290					295				Ī	300				Gly.	
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Trp	Phe	Ala	Asn 20	Asn	Ala	Gly	Leu	Lys 25	Arg	Glu	Lys	Asp	G1n 30	Ser	Lys	
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Gln	Val	Va1 35	Val	Glu	Ser	Leu	Tyr 40	He	He	Ser	Cys	Tyr 45	Gly	Thr	Leu	٠

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									gaa Glu 90						288
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	-								gga Gly						384
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									ttc Phe 170						528
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-	-		-			_			atc Ile						672

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358

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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
                            120
Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
                       135
                                           140
Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
145
                    150
                                        155
His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
                                    170
Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Ser Val Leu Gln
                                185
Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
                            200
                                                205
Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
                        215
                                            220
Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Arg Gly
                    230
                                        235
Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
                                   250
                245
Thr Leu Leu Glu Val Cys Gly Ser Trp Pro Glu Gly Phe Gly Leu Arg
                                265
His Met Ser Ser Met Glu His Thr Glu Glu Gly Ser Gly Ser Asp Leu
                            280
Pro Thr Pro Trp Pro Ser His Leu Ala Gly Thr Ser Trp Asp Pro Glu
                        295
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Gln Thr Gln Pro Leu Thr
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										agc Ser						144
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										cag Gln 75						240
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	-	-		_	-	-	-	_	-	ccc Pro		Lys	-	-	-	336
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Arg Tyr Glu Pro Ser Asp Lys Asp Arg Gln Ser Pro Pro Pro Ala Lys
Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
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Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
Ser Lys Ser Ser Ser Lys Val Thr Ser Val Pro Gly Lys Ala Ser Asp
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Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
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Arg Lys Arg Ala Lys Ile Pro Gly Lys Ala
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Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
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1
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ctc ctc gca ggg ctt gca cta ctg gga gtc ggg ccg gtc cca gcg cgg
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Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
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			30					25					20			
144		tgg Trp	-		-					-	-	-			_	
192		gat Asp	_	-	-					-			-			
240	-	gac Asp	-	_					-		_	-		_		
288		aat Asn 95	-			_	-	_							_	
336	tct. Ser	gat Asp		-		_			-	-	-			_	_	-
384	_	aag Lys	-								-		-	_	-	
432		gat Asp										-	-	-		
480		cta Leu			-									_		
528		aca Thr 175					-				-				-	_
576		tgg Trp									_		_			_
624	-	cat His					-	-		-				-	_	

		195					200					205				
		-	_		_	-		aca Thr	-	_			_	_		672
-		-						cag Gln					-		_	720
_					-	_		ata Ile	_	-					-	768
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				_			-	gaa Glu				-		_	-	864
					_			atg Met	_	-		-		-		912
					_			ctc Leu								960
	•	-				-		cca Pro								1008
								cca Pro 345							-	1056
								gcc Ala								1104
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	ttt Phe	_			-	-						_		Ser	1248
	gga Gly			_		_		-							1296
	gaa Glu	-	-	-			-					-		-	1344
-	tct Ser 450		-	-		_	-								1392
	gga Gly				_									-	1440
	aat Asn			-									-		1488
	cta Leu														1536
-	cat His			-				•			_				1584
_	aaa Lys 530					_								_	1632
	cca Pro					-		-						tat Tyr	1680

364

545 550 555 560 ctt aca cca agt aat att gtt ctg ctt act gct ata gct ctc atc ggt 1728 Leu Thr Pro Ser Asn Ile Val Leu Leu Thr Ala Ile Ala Leu Ile Gly 570 565 575 gtc tgt gtt ttc atc ttg gca ata att ggc att tta cat tgg cag gaa 1776 Val Cys Val Phe Ile Leu Ala Ile Ile Gly Ile Leu His Trp Gln Glu 580 585 590 aag aaa gca gat gat aga gaa aaa cga caa gaa gcc cac cgg ttt cat 1824 Lys Lys Ala Asp Asp Arg Glu Lys Arg Gln Glu Ala His Arg Phe His ttt gat gct atg tga 1839 Phe Asp Ala Met \* 610 <210> 246 . <211> 612 <212> PRT <213> Homo sapiens <400> 246 Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro 5 10 15 Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg 25 Ala Leu His Asn Val Thr. Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly 40 Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu 55 60 Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln 70 75 Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His 90 Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser 100 105 Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser 120 125 Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro 135 Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile

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Glu	Ser	Asn	Gln 180	Pro	Gln	Ile	Leu	Leu 185	Gly	Gly	Asn	Leu	Ser 190	Trp	His
Pro	Ala	Leu 195	Thr	Thr	Thr	Ser	Lys 200	Met	Arg	Ile	Pro	His 205	Ser	His	Ala
Phe	Ile 210	Asp	Leu	Thr	Glu	Asp 215	Phe	Thr	Ala	Asp	Leu 220	Phe	Leu	Thr	Thr
Leu 225		Αla	Thr	Thr	Ser 230	Thr	Phe	Gln	Phe	G1u 235	Пe	Trp	Glu	Asn	Leu 240
Asp	Gly	Asn	Phe	Ser 245	Val	Ser	Thr	Ile	Leu 250	Glu	Lys	Pro	Gln	Asn 255	Met
Met	Val	Val	Gly 260	Gln	Ser	Ala	Phe	Ala 265	Asp	Phe	Asp	Gly	Asp 270	Gly	His
Met	Asp	His 275	Leu	Leu	Pro	Gly	Cys 280	Glu	Asp	Lys	Asn	Cys 285	Gln	Lys	Ser
Thr	Ile 290	Tyr	Leu	Val	Arg	Ser 295	Gly	Met	Lys	Gln	Trp 300	Val	Pro	Val	Leu
G1n 305	Asp	Phe	Ser	Asn	Lys 310	Gly	Thr	Leu	Trp	Gly 315	Phe.	Val	Pro	Phe	Val 320
Asp	Glu	G1n	Gln	Pro 325	Thr	Glu	IJе	Pro	Ile 330	Pro	Пe	Thr	Leu	His 335	IJе
Gly	Asp	Tyr	Asn 340	Met	Asp	Gly	Tyr	Pro 345	Asp	Ala	Leu	Val	Ile 350	Leu	Lys
Asn	Thr	Ser 355	Gly	Ser	Asn	Gln	G1n 360	Ala	Phe	Leu	Leu	G1u 365	Asn	Val	Pro
Cys	Asn 370	Asn	Ala	Ser	Cys	G1u 375	Glu	Ala	Arg	Arg	Met 380	Phe	Lys	Val	Tyr
385				1	390	Asn				395					400
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Lys	Gly	Tyr	Thr 420	Lys	Asn	Asp	Phe	Ala 425	He	His	Thr	Leu	Lys 430	Asn	Asn
Phe	Glu	Ala 435	Asp	Ala	Tyr	Phe	Val 440	Lys	Val	Ile	Val	Leu 445	Ser	Gly	Leu
Cys	Ser 450	Asn	Asp	Cys	Pro	Arg 455	Lys	Пe	Thr	Pro	Phe 460	Gly	Val	Asn	Gln
Pro 465	Gly	Pro	Tyr	Пе	Met 470	Tyr	Thr	Thr	Val	Asp 475	Ala	Asn	Gly	Tyr	Leu 480
Lys	Asn	Gly	Ser	A1a 485	Gly	Gln	Leu	Ser	G1n 490	Ser	Ala	His	Leu	Ala 495	
Gln	Leu	Pro	Tvr	Asn	Val	Leu	Glv	Len		Δra	Ser	Δla	Δsn		Leu

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Asp	His	Leu 515	Tyr	Val	Gly	Ile	Pro 520	Arg	Pro	Ser	Gly	G1u 525	Lys	Ser	Ile	
Arg	Lys 530	Gln	Glu	Trp	Thr	A1 a 535	Ile	Ile	Pro	Asn	Ser 540	Gln	Leu	Ile	Val	
I le 545	Pro	Tyr	Pro	His	Asn 550	Val	Pro	Arg	Ser	Trp 555	Ser	Ala	Lys	Leu	Tyr 560	
Leu	Thr	Pro	Ser	Asn 565	Ile	Val	Leu	Leu	Thr 570	Ala	Ile	Ala	Leu	11e 575	Gly	
Val	Cys	Val	Phe 580	Ile	Leu	Ala	Ile	11e 585	Gly	Ile	Leu	His	Trp 590	Gln	Glu	
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		-										agc Ser 45	-	-	-	144
												act Thr				192
	aga Arq	-	-				-			-	-	ttt Phe				240

65					70					75					80	
					gtg Val											288
		_			tca Ser	_										336
	-	-		-	ttc Phe											384
					cag Gln											432
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											cgc Arg 60					192
											ctc Leu					240
											aag Lys					288

	aca Thr														336
	gct Ala														384
	tct Ser 130		-							_		_	_	-	432
	cca Pro	-			_	_	-			-				_	480
_	aca Thr				_		_	_		-	_				528
	aag Lys		-		-										576
	gat Asp														624
	ctg Leu 210														672
	agg Arg														720
	gcg Ala														768
-	acc Thr			_					-			_			816

											cag Gln					. 864
											tcc Ser 300					912
											cgt Arg					960
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Cys	Va1 50		Gln	Phe	Asp	Pro 55		Leu	Leu	Glu	Arg 60		Leu	Val	Cys	

Ala 65	Pro	Glu	Ser	Leu	His 70	Thr	Val	His	Ala	Ala 75	Leu	Ile	Ser	Val	Glu 80
Lys	Ile	Pro	Tyr	Phe 85	Arg	Gly	Pro	Leu	G1n 90	Thr	Lys	Ala	Lys	Phe 95	His
Пe	Thr	Val	Gly 100	His	Glu	Thr	Val	Met 105	Gly	Arg	Leu	Met	Phe 110	Phe	Ser
Pro	Ala	Pro 115	Asp	Asn	Phe	Asp	Gln 120	Glu		Ile	Leu	Asp 125	Ser	Phe	Asn
Phe	Ser 130	Gln	Glu	Tyr	Leu	Phe 135	Gln	Glu	Gln	Tyr	Leu 140	Ser	Lys	Asp	Leu
Thr 145	Pro	Ala	Val	Thr	Asp 150	Asn ·	Asp	Glu	Ala	Asp 155	Lys	Lys	Ala	Gly	Gln 160
				165	-				170	·			Val	175	
Glu	Lys	Pro	Val 180	Thr	Cys	Pro	Arg	Leu 185	Cys	Leu	Val	He	Gly 190	Ser	Arg
Leu	Asp	Ala 195	Asp	Пe	His	Thr	Asn 200	Thr	Cys	Arg	Leu	Ala 205	Phe	His	Gly
Пe	Leu 210	Leu	His	Gly	Leu	G1u 215	Asp	Arg	Asn	Tyr	Ala 220	Asp	Ser	Phe	Leu
225					230	_				235			Leu		240
-				245					250				Phe	255	
			260					265					Leu 270		
		275					280					285	Gly	•	
	290					295					300		Lys		
305					310					315			Glu		320
Arg	Gln	Glu	Glu	Ser 325	Ala	Glu	Arg	Xaa	Xaa 330	Pro	Ser	Gln	His	Va1 335	۷a۱
Leu	Ser	Leu	Thr 340	Phe	Lys	Arg	Tyr	Val 345	Phe	Asp	Thr	His	Lys 350	Arg	Met
Val	Gln	Ser 355	Pro												
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	-														

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cgg Arg									-		_	_	96
aat Asn					_	-			 -		_		144
cag Gln 50			-					_					192
aac Asn										_	-	-	240
gtg Val													.288
agt Ser												_	336
ttt Phe													384
aag Lys 130					_			-	 -	-	_	_	432
gaa Glu							_				-		480

528 atg acg acg tcc ttc tgg aag agg cga aac tgg tac gtt gat gat cct Met Thr Thr Ser Phe Trp Lys Arg Arg Asn Trp Tyr Val Asp Asp Pro 170 165 tat cag aag tat cat gat cga aca aac ctg aaa gta tag 567 Tyr Gln Lys Tyr His Asp Arg Thr Asn Leu Lys Val \* 180 185 <210> 252 <211> 188 <212> PRT <213> Homo sapiens <400> 252 Met Ala Ala Ser Ala Phe Ala Gly Ala Val Arg Ala Ala Ser Gly Ile 10 Leu Arg Ser Leu Asn Ile Leu Ala Ser Ser Thr Tyr Arg Asn Cys Val Lys Asn Ala Ser Leu Ile Ser Ala Leu Ser Thr Gly Arg Phe Ser His 40 45 Ile Gln Thr Pro Val Val Ser Ser Thr Pro Arg Leu Thr Thr Ser Glu 55 60 Arg Asn Leu Thr Cys Gly His Thr Ser Val Ile Leu Asn Arg Met Ala 70 Pro Val Leu Pro Ser Val Leu Lys Leu Pro Val Arg Ser Leu Thr Tyr Phe Ser Ala Arg Lys Gly Lys Arg Lys Thr Val Lys Ala Val Ile Asp 100 105 Arg Phe Leu Arg Leu His Cys Gly Leu Trp Val Arg Arg Lys Ala Gly 120 Tyr Lys Lys Leu Trp Lys Lys Thr Pro Ala Arg Lys Lys Arg Leu 135 Arg Glu Phe Val Phe Cys Asn Lys Thr Gln Ser Lys Leu Leu Asp Lys 150 155 Met Thr Thr Ser Phe Trp Lys Arg Arg Asn Trp Tyr Val Asp Asp Pro 165 170 175 Tyr Gln Lys Tyr His Asp Arg Thr Asn Leu Lys Val 180 185 <210> 253 <211> 453

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			gta Val												144
			ggt Gly		_					_	_	-		-	192
			aag Lys												240
_	-	_	cca Pro		-	-	-	_		_		_	_		288
			tcc Ser 100	_	-		-	_	_			_	_		336
	-		gaa Glu		-	_		-		_	_	-	_		384
			gct Ala	-	_						_			_	432
gga	aag	aag	gat	aaa	cgt	taa									453

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Leu Leu Ser Phe Leu Phe Ile Asn Lys Ile Phe Arg Arg Lys Thr Phe
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Glu Glu Val Val Ala Glu Lys Arg Ala Leu Ser Ala Asn Leu Tyr Lys
Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Glu Leu Lys
                                            60
                        55
Arg Glu Lys Lys Gln Arg Gln Arg Glu Gln Gln Arg Asp Val Asn Asn
                    70
                                        75
Glu Pro Glu Pro Glu Glu Ala Glu Asp Tyr Ser Asp Gly Gln Ser Glu
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Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
                                105
Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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Ser Ser Val Ala Glu Lys Glu Asn Gln Pro Ser Gly Ala Gly Lys Lys
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Gly Lys Lys Asp Lys Arg
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Met Ala Phe Leu Ser Pro Leu Val Leu Ile Cys His Pro Thr His Phe
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                                                         15
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				atg Met								96
				gat Asp								144
				aaa Lys								192
				cct Pro 70								240
				gtt Val								288
				ctc Leu								336
				ata Ile								384
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				agc Ser 150								480
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96

377

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20 . 25 30

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_						_		_		-	_	_	cag Gln	_	192
	-		•		_		-			-		_	cgg Arg		240
													act Thr 95		. 288
				•			_	_	_	-			ctt Leu		. 336
	Asp												ctt Leu		384
	•										_		gac Asp		432
	-	_				att Ile							acc Thr	taa *	480

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<400> 258

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His	Cys	Thr 35	Val	Pro	Ala	Tyr	Asn 40	Phe	Pro	Val	Thr	Ala 45	Met	Ala	Ile	
Ala	Pro 50		Thr	Asn	Asn	Leu 55	Val	Ile	Ala	His	Ser 60	Asp	Gln	Gln	Val	
Phe 65	Glu	Tyr	Ser	Ile	Pro 70		Lys	Gln	Tyr	Thr 75	Asp	Trp	Ser	Arg	Thr 80	
	Gln	Lys	Gln	G1 <i>y</i> 85		His	His	Leu	Trp 90	Leu	Gln	Arg	Asp	Thr 95	Pro	
Пe	Thr	His	Ile 100	Ser	Phe	His	Pro	Lys 105	Arg	Pro	Met	His	Ile 110	Leu	Leu	
His	Asp	Ala 115	Tyr	Met	Phe	Cys	Ile 120	Пe	Asp	Lys	Ser	Leu 125	Pro	Leu	Pro	
Asn	Asp 130	Lys	Thr	Leu	Leu	Tyr 135	Asn	Pro	Phe	Pro	Pro 140	Thr	Asn	Asp	Ile	
I1e 145	Ala	Gln	Leu	Pro	Pro 150	Pro	Ile	Lys	Lys	Lys 155	Lys	Phe	Gly	Thr		
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	ctt Leu															144
_	ggc Gly 50			_	_	-										192
cag	cat	ctg	aga	gaa	agg	gat	tcc	aaa	cta	tac	ctc	cat	gag	ctc	cta	240

G1n - 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
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														gcc Ala		336
	_						_		-		_	-	-	aca Thr	-	384
		000			_	_	-		-			_		ttg Leu	-	432
														gct Ala	gcc Ala 160	480
	_	_					-						_	atg Met 175	-	528
														ctg Leu		576
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taa *																627

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<211> 208

<212> PRT

<213> Homo sapiens

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Glu	Leu	G1u 35	Ala	Ala	Leu	Gly	Lys 40	Lys	His	Lys	Gly	Gly 45	Asp	Ser	Ser	
Ser	Gly 50	Pro	G1n	Arg	Leu	Va1 55	Ser	Phe	Arg	Leu	Ile 60	Arg	Asp	Leu	His	
G1n 65	His	Leu	Arg	Glu	Arg 70	Asp	Şer	Lys	Leu	Tyr 75	Leu	His	Glu		Leu .80	
Glu	Gly	Ser	Glu	Ile 85	Tyr	Leu	Pro	Glu	Va1 90	Val	Lys	Pro	Pro	Arg 95	Asn	
	Glu		100		_	•		105	•	•			110			
	Glu	115					120					125				
His	Gly 130	Gly	Thr	Leu	Ser	Asp 135	Leu	Gly	Lys	Gln	Val 140	Arg	Ser	Leu	Lys	
Ala 145	Leu	Val	He	Thr	11e 150	Phe	Asn	Phe	Ile	Val 155	Thr	Val	Val	Ala	Ala 160	
Phe	Val	Cys	Thr	Tyr 165		Gly	Ser	Gln	Tyr 170	Пe	Phe	Thr	Glu	Met 175	Ala	
Ser	Arg	Val	Leu 180	Ala	Ala	Leu	He	Val 185	Ala	Ser	Val	۷al	Gly 190	Leu	Ala	
Glu	Leu	Tyr 195	Val	Met	Val	Arg	Ala 200	Met	Glu	Gly	Glu	Leu 205	Gly	Glu	Leu	
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	gcc Ala															70
gcc	cgc	tcc	ctc	tcg	cgc	ttc	cga	ggc	tgc	ctg	gct	ggc	gcg	ctg	ctc	96

Ala	Arg	Ser	Leu 20	Ser	Arg	Phe	Arg	Gly 25	Cys	Leu	Ala	Gly	Ala 30	Leu	Leu	
		_									_		-	gac Asp	_	144
_		-	_	-		_	_	_	_		_	-		ggc Gly	_	192
		_				-	_	_				_	_	aca Thr	_	240
_	-		_	_		_		_		-	_		_	ttt Phe 95	•	288
		-		-		-			-			_		gac Asp		336
					-							-	_	ctc Leu	_	384
			_	-	-	-				-		-	-	ttt Phe		432
														ggc Gly		480
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														gcc Ala		576
ctg	cag	gcc	ctg	gct	gtg	cac	ctg	gcc	ttg	cag	ggc	gag	tct	tcc	agc	624

Leu	Gln	Ala 195	Leu	Ala	Val	His	Leu 200	Ala	Leu	Gln	Gly	G1u 205	Ser	Ser	Ser	
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														gag Glu	_	720
			_	-	_	_	_						-	cag Gln 255	•	768
													-	att Ile	-	816
-			_	-			-			_			•	tgc Cys	_	. 864
		-						_			_			agg Arg		912
									-		-			gcc Ala		960
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Leu 305		Tyr	Ser	Пe	Ser 310	Leu	Gly	Gly	Asp	Thr 315	Asp	Thr	Пe	Ala	Thr 320	
		Gly	Ala	I1e 325		Gly	Ala	Tyr	Tyr 330		Met	Asp	Gln	Va1 335		
		·	340					345	•		Glu	Thr	Asp 350	Ile	Leu	
Ala	. G1n	Ser 355	Leu	His	Arg	Val	Phe 360	Gln	Lys	Ser						
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													-	cag Gln	_	144
														ctg Leu	_	192
				Gln										ctg Leu		240
								-				-	-	ctg Leu 95		288
cga	999	gag	cta	cag	cga	gtc	сса	acc	ctg	cta	ctg	ссс	atg	cct	acg	336

Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr		
					acc Thr												384
		~ ~	_		gac Asp			_						_			432
					cgg Arg 150												480
					ctc Leu												528
		_	_		ttc Phe												576
					gtg Val										cct Pro	••	624
					ctc Leu												672
			-		tat Tyr 230	-			-	_				-	-		720
					ctc Leu												768
					acc Thr												816
gga	gcc	ttg	cga	gct	ctg	agc	ctg	cct	ctg	acc	cag	ttg	cct	gtg	tcc		864

Gly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	
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													cgt Arg			960
													ttc Phe			1008
													cgc Arg 350			1056
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<211> 412

<212> PRT

<213> Homo sapiens

<400> 264

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Glu	Arg	Thr 35	Ser	Gly	Gly	Pro	G1u 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Ser	Leu 50	Gly	Ser	Ser	Arg	Va1 55	Pro	Arg	Cys	Gly	Gln 60	Gly	Thr	Leu	Leu
65			·		70					75		·	-	Leu	80
His	Cys	Ser	Pro	A1a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
	, -		100					105					110	Pro	
		115					120					125		Arg	
	130	_			·	135					140			Asp	
145	•				150					155				Glu	160
•				165		•			170					Leu 175	
J			180					185					190	Glu	
		195					200					205		Gln	
	210					215		·		_	220		•	Leu	
225					230					235				Ala	240
		·	•	245			•		250					Leu 255	
·	_		260				_	265					270	His	
-		275					280					285		Val	
	290					295			·		300			Leu	
305	•		·		310			·		315				Trp	320
Pro	Val	Leu	Tyr	A1a 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	Ile 335	Phe
		·	340				·	345					350	Arg	
Met	Leu	G1n 355	Lys	Thr	Trp	Leu	Leu 360	Ala	Asp	Glu	Gly	Leu 365	Arg	Gln	His

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					gcc Ala									96
					cac His	-								144
-			_		ttc Phe	-	_							192
					gga Gly 70									240
					ctg Leu									288
				_	agg Arg	_		-						336

	tgc Cys			_	-			_	-		-		_		•	384
	gct Ala 130										-		-		_	432
	atg Met															480
	ccc Pro	-		_			-			-	_			_	_	528
	gat Asp				-							-			tga *	576
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Cys	Ala	Ala	Leu 20		Ala	Trp	Pro	Ala 25		G1n	Пe	Ala	Va1 30		Asn	
Gly	Phe	Gly 35		Val	His	Ser			_	Ala	Lys	Trp 45		Gly	Gly	
Ala	Va1 50	Glu	Asp	Tyr	Phe	Met 55	Arg	Asn	Ala	Asp	Leu 60	Glu	Leu	Asp	Glu	
Val 65	Glu	Asp	Phe	Leu	Gly 70		Leu	Leu	Thr	Asn 75		Phe	Asp	Thr	Val 80	
	Glu	Asp	Gly	Ser 85		Pro	Gln	Val	Ser 90		Gln	Leu	Gln	Thr 95		
Phe	His	His	Phe 100		Arg	Gly	Asp	Gly 105		Ala	Leu	Arg	Glu 110		Ala	
Ser	Cys	Ile		Gln	Arg	Lys	Cys		Val	Thr	Ala	Thr		Leu	Lys	

Thr	Ala 130	Arg	Glu	Thr	Asp	G1u 135	Asp	Glu	Asp	Asp	Val 140	Asp	Ser	Val	Glu	
G1u 145		Glu	Val	Thr	Ala 150	Thr	Asn	Asp	Gly	Ala 155	Ala	Thr	Asp	Gly	Val 160	
Cys	Pro	Gln	Pro	Glu 165	Pro	Ser	Asp	Pro	Asp 170	Ala	Gln	Thr	Пe	Lys 175	G1u	
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		_	_			-		-			ttc Phe		_			144
-	-	-									tat Tyr 60		-			192
				_							gaa G1u		-			240
											agg Arg					288
ttc	ctc	tcc	aag	act	cgg	gtg	gtc	cag	gag	cac	ggc	999	cgg	gcg	gtg	336

Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105	Glu	His	Gly	Gly	Arg 110	Ala	Val	
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	-	-	-		-	_		-	-		ccc Pro 140	-			_	432
											ctg Leu					480
•			•						-		gtc Val		_			528
			_	_		•			acc Thr		tgg Trp	tag *				567
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Ala	Cys	Val	A1a 20	Ala	His	Gly	Phe	Arg 25	Ile	His	Asp	Tyr	Leu 30	Tyr	Phe	
Gln	Val	Leu 35	Ser	Pro	Gly	Asp	Ile 40	Arg	Tyr	Пе	Phe	Thr 45	Ala	Thr	Pro	
Ala	Lys 50	Asp	Phe	Gly	Gly	Ile 55	Phe	His	Thr	Arg	Tyr 60	Glu	Gln	Ile	His	
	Val	Pro	Ala	Glu		Pro	Glu	Ala	Cys		Glu	Leu	Ser	Asn	_	
65 Phe	Phe	Ile	Gln	Asp 85	70 G1n	Ile	Ala	Leu	Val 90	75 Glu	Arg	Gly	Gly	Cys 95	80 Ser	
Phe	Leu	Ser	Lys 100		Arg	Val	Val	Gln 105		His	Gly	Gly	Arg 110		Val	

He	He	Ser 115	Asp	Asn	Ala	Val	Asp 120	Asn	Asp	Ser	Phe	Tyr 125	Val	Glu	Met	
Пe	Gln 130		Ser	Thr	Gln	Arg 135	Thr	Ala	Asp	He	Pro 140	Ala	Leu	Phe	Leu	
Leu 145	Gly	Arg	Asp	Gly	Tyr 150	Met	Ile	Arg	Arg	Ser 155	Leu	Glu	Gln	His	Gly 160	
Leu	Pro	Trp	Ala	Ile 165	Ile	Ser	Ile	Pro	Val 170	Asn	Val	Thr	Ser	Ile 175	Pro	
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														gag G1u		192
_														agc Ser		240
-			-				_		-	-				ccg Pro 95	-	288

aac	ctc	tat	ata	,	C22	aaa	cat	uac	aaa	acc	aca	ac a	aca	taa	Cau	336
	Leu			_								-			_	330
-	999 Gly			•	-	•	-		_	-					•	384
	tct Ser 130			-			_		_		-		_		-	432
-	agt Ser	_				_	-	-	-		_	_	_			480
	cag Gln															528
	acc Thr	_		_			_				-	-	_	_		576
	ctc Leu		_	-												624
	aag Lys 210															672
	gcc Ala															720
	tcc Ser															768
	att Ile	_		_												816

						-							tat Tyr	_	864
		-		_	_	-	_						ctt Leu	•	912
_		-		_		-		_					ttc Phe		960
	_		_	_		-	-	-				_	cat His 335		1008
		-		-									aac Asn		1056
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Ser	Ser	Arg 35	Trp	Ser	Glu	Leu	Asp 40	Leu	Leu	Пе	Leu	Leu 45	Gly	Thr	Ala	
Gly	His 50	Val	Leu	Ser	Leu	Gly 55	Ala	Ser	Ser	Phe	Va1 60	Glu	Glu	Glu	His	
G1n 65	Thr	Trp	Tyr	Phe	Leu 70	Val	Asn	Thr	Leu	Cys 75	Leu	Ala	Leu	Ser	G1n 80	
Glu	Thr	Tyr	Arg	Asn 85	Tyr	Phe	Leu	Gly	Asp 90	Asp	Gly	Glu	Pro	Pro 95	Cys	
Gly	Leu	Cys	Val 100	Glu	Gln	Gly	His	Asp 105	Gly	Ala	Thr	Ala	Ala 110	Trp	Gln	
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Pro	Ser 130	Thr	Ser	Glu	Val	Leu 135	Arg	Gly	Arg	Glu	Lys 140	Trp	.Met	Val	Leu	
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145 Asn	Gln	Thr	Glv	Val	150 Gln	Trp	Ala	His	Ara	155 Pro	Asp	Leu	Glv	His	160 Trp	
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Leu	Thr	Ser	Ser 180	Asp	His	Lys	Ala	G1u 185	Leu	Ser	Val	Leu	Ala 190	Ala	Leu	
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Ser	Lys 210	Ala	Ala	Leu	Ala	Leu 215	Gly	Leu	Leu	Gly	Va1 220	Tyr	Cys	Tyr-	Arg	

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Ala Ala Ile Gly Ser Val Arg Phe Pro Trp Arg Pro Asp Ser Lys Asp
225
                    230
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Ile Ser Lys Gly Ile Ile Glu Ala Arg Phe Val Tyr Val Phe Val Leu
                245
                                    250
Gly Ile Leu Phe Thr Gly Thr Lys Asp Leu Leu Lys Ser Gln Val Ile
                                265
Ala Ala Asp Phe Lys Leu Lys Thr Val Gly Leu Trp Glu Ile Tyr Ser
                            280
Gly Leu Val Leu Leu Ala Ala Leu Leu Phe Arg Pro His Asn Leu Pro
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Val Leu Ala Phe Ser Leu Leu Ile Gln Thr Leu Met Thr Lys Phe Ile
                    310
                                        315
Trp Lys Pro Leu Arg His Asp Ala Ala Glu Ile Thr Val Met His Tyr
                325
                                    330
Trp Phe Gly Gln Ala Phe Phe Tyr Phe Gln Gly Asn Ser Asn Asn Ile
                                345
Ala Thr Val Asp Ile Ser Ala Gly Phe Val Gly Leu Asp Thr Tyr Val
                            360
Glu Ile Pro Ala Val Leu Leu Thr Ala Phe Gly Thr Tyr Ala Gly Pro
                        375
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Val Leu Trp Ala Ser His Leu Val His Phe Leu Ser Ser Glu Thr Arg
                    390
                                        395
Ser Gly Ser Ala Leu Ser His Ala Cys Phe Cys Tyr Ala Leu Ile Cys
                405
                                    410
Ser Ile Pro Val Phe Thr Tyr Ile Val Leu Val Thr Ser Leu Arg Tyr
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                                425
His Leu Phe Ile Trp Ser Val Phe Ser Pro Lys Leu Leu Tyr Glu Gly
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-	_	_							_	_			-	tca Ser	-	240
_				-		-	_							ctc Leu 95		288
_	_	_	_	_										atc Ile		336
			-	-										acc Thr		384
_			-			_								tcc Ser		432
_								_						gca Ala		480.
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WO 01/29221

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			-				-			_	aac Asn	_			_	624
				_		_	_				gct Ala 220		_	_		672
_			_								ctc Leu					720
	-			-		-	-				atc Ile		-	-	_	768
	-	-		_				-		-	gta Val		-		_	816
-					-	-	-		-		gcc Ala	-			_	864
_	_		_	_	_		_	_		_	acc Thr 300	_	-		_	912
-				-	_	-	_			-	ccc Pro			-		960
											gac Asp					1008
gac	acc	tgg	ctg	gcc	agc	cgc	gtg	ссс	tgc	ссс	acc	tgc	cgc	gca	cgc	1056

400

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Leu	Leu 210	Thr	Пe	Arg	Val	Ala 215	Ser	Thr	Asn	Pro	Ala 220	Val	Gln	Ala	Phe	
Asp 225	Ile	Trp	Leu	Asn	Ser 230	Thr	Glu	Tyr	Gly	G1u 235	Leu	Cys	Glu	Lys	Leu 240	
Arg	Ala	Pro	Пe	Arg 245	Arg	Ala	Ala	His	Va1 250	Val	Ile	His	Gln	Ser 255	Leu	
Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	A1 a 265	Ser	Leu	Val	Glu	Va1 270	Asn	Pro	
Ala	Tyr	Ser 275	Val	Pro	Ser	Ser	Gln 280	Glu	Leu	Glu	Ala	Cys 285	Ile	Gly	Cys	
Met	G1n 290	Thr	Arg	Ala	Ser	Val 295	Lys	Leu	Val	Lys	Thr 300	Cys	Gln	Glu	Ala	
Ala 305	Thr	Gly	Glu	Cys	Gln 310	Gln	Cys	Tyr	Cys	Arg 315	Pro	Met	Trp	Cys	Leu 320	
Thr	Cys	Met	Gly	Lys 325	Trp	Phe	Ala	Ser	Arg 330	Gln	Asp	Pro	Leu	Arg 335	Pro	
Asp	Thr	Trp	Leu 340	Ala	Ser	Arg	Val	Pro 345	Cys	Pro	Thr	Cys	Arg 350	Ala	Arg	
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_	cca Pro			_		-	-	_								144

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										cac His		38	4
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										gac Asp 190		57	6
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Cla Das La	20 . Dha Ana	. 01 41.		25	Tum	۸۵۵	Dha	۸1 -	30	Mat	110	
Gln Pro Lei 35	i Prie Arg	J GIY AIC	40	Arg	Tyr	ASÞ	rne	45	116	met	He	
Pro Pro Gl	Gly Thr	Glu Cys		Trp	Gln	Phe	Ala		Gln	Thr	Gly	
50		55		0.7		~.	60	03		_		
Tyr Phe Tyr 65	he Ser	r Tyr Glu 70	Vai	Gin	Arg	inr 75	vaı	Gly	met	Ser	нтs 80	
Asp Arg Hi:	. Val Ala		Ala	His	Asn		Gln	Glv	Phe	Leu		
7.0p 7.11 g 11.11	85				90			- J		95		
Asp Thr Se	_	/ Val Arg	Gly		Пe	Asn	Phe	Ser		Gln	Glu	
The Cly Ob	100	Lau Cyc	Lou	105	۸cn	Gln	Uic	Acn	110	Dho	Gly	
Thr Gly Pho	-	r Leu cys	120	261	ASII	um	1112	125	1112	rile	diy	
Ser Val Gl		Leu Asr		Gly	۷a٦	Phe	Tyr		Gly	Pro	Glu	
130		135					140	_				
Thr Asp His	Lys Gln		Arg	Lys	GIn		Asn	Asp	Ihr	Leu		
145 · Ala Ile Gli	L Asn Gly	150 The Gle	Lvc	Val	Gln	155 Asn	Δcn	۵۱۱	Pho	Hic	160 Met	
Ald Tie un	165		Lys	vui	170	7311	ASII	110	TIIC	175	1100	
Trp Arg Ty			Arg	Met	Arg	Lys	Met	Ala	Asp	Phe	Phe	
	180	<b>~</b> .	-	185		<b>T</b>	<b>-</b>	<b>.</b>	190	47 -	01 -	
Leu Ile Gli 19		ı ıyr Asr	1yr 200	val	ASN	ırp	ırp	Ser 205	ınr	Ala	GIN	
Ser Leu Va		Leu Ser		Пe	Leu	Gln	Leu		Phe	Leu	Lys	
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Arg Leu Ph	e Asn Val	Pro Thr	Thr	Thr	Asp	Thr	Lys	Lys	Pro	Arg	Cys	

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										ctg Leu		240
										ctc Leu 95		288
										cca Pro		336

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												ttc Phe			720
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	_			_	_							gag G1u 270			816
-	Αla	-	-		-							cac His			864

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1	Ala	Glu	His His	5	•	Pro Ala		Glu	10				Thr	15		
1 Ala	Ala Cys	Glu Thr Leu	His His 20	5 Ser	Ser		Tyr Asn	G1u 25	10 Asn	Gln	Arg	Val Asn	Thr 30	15 Thr	Thr	
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1 Ala Ala Leu Cys 65 Ser	Ala Cys Phe Leu 50 Ala Gly Met	Glu Thr Leu 35 Asp Xaa Cys Ile	His 20 Ala Ser Val Pro Gly 100	5 Ser Glu Leu Arg Asp 85 Gly	Ser Leu Leu Arg 70 Lys Leu	Ala Leu Glu 55 Leu Val	Tyr Asn 40 Ser Val Arg Asp	Glu 25 Ser Leu Leu Thr Gly 105	10 Asn Ala Arg His 90 Asp	Gln Val Ala Gly 75 Gly Asn	Arg Ala Arg 60 Leu Pro	Val Asn 45 Gln Ala Gln His	Thr 30 Asp Lys Asn Leu Ser 110	15 Thr Leu Asp Leu Leu 95 Pro	Thr Met Thr Ala 80 Thr	•
1 Ala Ala Leu Cys 65 Ser Ala	Ala Cys Phe Leu 50 Ala Gly Met Leu	Glu Thr Leu 35 Asp Xaa Cys Ile Glu 115	His 20 Ala Ser Val Pro Gly 100 Ala	5 Ser Glu Leu Arg Asp 85 Gly Met	Ser Leu Leu Arg 70 Lys Leu Leu	Ala Leu Glu 55 Leu Val	Tyr Asn 40 Ser Val Arg Asp Leu 120	Glu 25 Ser Leu Leu Thr Gly 105 Ala	Asn Asn Ala Arg His 90 Asp	Gln Val Ala Gly 75 Gly Asn Leu	Arg Ala Arg 60 Leu Pro Pro	Val Asn 45 Gln Ala Gln His His	Thr 30 Asp Lys Asn Leu Ser 110 Leu	15 Thr Leu Asp Leu 95 Pro Val	Thr Met Thr Ala 80 Thr Val	

Leu	Phe	Gly	His	Leu 165	Asn	Lys	Val	Cys	His 170	Gly	Asp	Cys	Glu	Asp 175	Val	
Phe	Leu	Asp	Gln 180		Val	Gly	Gly	Leu 185		Pro	Leu	Leu	Leu 190	His	Leu	
G1n	Asp	Pro 195		Ala	Thr	Val	Ala 200		Ala	Cys	Arg	Phe 205		Leu	Arg	
Met	Cys 210		Pro	Asn	Leu	Ala 215		Glu	Glu	Leu	Ser 220		Ala	Phe	Gln	
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Arg	Ala	A1a 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu	
Pro	Arg 290	Gln	Gln	Pro	Gln	Va1 295	Asp	Leu	Asp	Gln	Leu 300	Ile	Ala	Ala	Leu	
G1n 305	Ile	Leu	Leu	Lys	Asp 310	Pro	Ala	Pro	Glu	Val 315	Arg	Thr	Arg	Ala	Ala 320	
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_		_		_	_									cgc Arg	•	144

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	gtg Val		_	-	_				_			-		-	•		288
	atc Ile					_	-	-			-				-		336
	ctc Leu																384
	aaa Lys 130	_					-	-			-		_				432
-	ggc Gly	-	_				_	-		-		-	-	_			480
_	ctg Leu			_			_			_			•		•		528
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Asp Pro Arg Asp Val Lys Asn Met Asn Thr Trp Leu Leu Phe Leu Pro
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Leu Phe Pro Val Gln Val Gln Thr Leu Ile Val Val Ile Ile Gly Met
                    70
                                        75
Leu Val Leu Leu Leu Asp Phe Leu Gly Leu Val His Leu Gly Gln Leu
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Leu Ile Phe His Ile Tyr Leu Lys Ala Lys Lys Met Thr Thr Phe Glu
            100
                                105
Tyr Leu Ile Asn Asn Arg Lys Glu Glu Ser Ser Lys His Gln Ala Val
                            120
Arg Lys Asp Pro Tyr Val Gln Met Asp Lys Gly Val Leu Gln Gln Gly
                        135
Ala Gly Ala Leu Gly Ser Ser Ala Gln Gly Val Lys Ala Lys Ser Ser
                   150
                                        155
Leu Leu Ile His Lys His Leu Cys His Phe Cys Thr Ser Val Asn Gln
                                   170
Asp Gly Asp Ser Lys Ala Gln Glu Ala Asp Asp Ala Pro Ser Thr Ser
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Thr Leu Gly Leu Gln Gln Glu Thr Thr Glu Pro Met Lys Thr Asp Ser
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Ala Glu Ser Glu Asp
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	cct Pro															624
_	gat Asp 210	_														672
	gat Asp															720
	ctc Leu															768
	act Thr															816
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	ttg Leu 290															912
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gct	gca	cat	gaa	gct	gag	gaa	gaa	tct	gat	aat	att	gca	gaa	gac	ttc	1056

Ala	Ala	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe	
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					cac His						-	_			-	1152
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Пe	Glu	Ser 35	Leu	Arg	Asn	Ser	His 40	Ser	Ser	Ile	Ala	Glu 45	IJе	Gln	Lys	
Asp	Val 50	Glu	Tyr	Arg	Leu	Pro 55	Phe	Thr	Ile	Asn	Asn 60	Leu	Thr	Ile	Asn	
Ile 65	Asn	He	Leu	Leu	Pro 70	Pro	Gln	Phe	Pro	G1n 75	Glu	Lys	Pro	Val	Ile 80	
Ser	Val	Tyr	Pro	Pro 85	He	Arg	His	His	Leu 90	Met	Asp	Lys	Gln	G1y 95	Val	
Tyr	Val	Thr	Ser 100	Pro	Leu	Val	Asn	Asn 105	Phe	Thr	Met	His	Ser 110	Asp	Leu	
Gly	Lys	Ile 115	Ile	Gln	Ser	Leu	Leu 120	Asp	Glu	Phe	Trp	Lys 125	Asn	Pro	Pro	
Val	Leu 130	Ala	Pro	Thr	Ser	Thr 135	Ala	Phe	Pro	Tyr	Leu 140	Tyr	Ser	Asn	Pro	
Ser 145		Met	Ser	Pro	Tyr 150		Ser	Gln	Gly	Phe 155	Pro	Phe	Leu	Pro	Pro 160	
	Pro	Pro	Gln	G1u 165	Ala	Asn	Arg	Ser	Ile 170		Ser	Leu	Ser	Val 175		

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Pro 225		Val	Pro	Asp	Ala 230		Pro	Glu	Leu	Ser 235		Leu	Ser	Val	Ser 240		
Gln	Leu	Thr	Asp	Met 245	Asn	G1u	Gln	Glu	G1u 250	Val	Leu	Leu	Glu	G1n 255	Phe		
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Val	Lys	Ser 275	Ile	Glu	Glu	Leu	Ala 280	Arg	Lys	Asn	Leu	Leu 285	Leu	Glu	Pro		
Ser	Leu 290	Glu	Ala	Lys	Arg	G1n 295	Thr	Val	Leu	Asp	Lys 300	Tyr	Glu	Leu	Leu		
Thr 305	Gln	Met	Lys	Ser	Thr 310	Phe	Glu	Lys	Lys	Met 315	Gln	Arg	Gln	His	G1u 320		
Leu	Ser	Glu	Ser	Cys 325	Ser	Ala	Ser	Ala	Leu 330	Gln	Ala	Arg	Leu	Lys 335	Val		
Ala	Ala	His	G1u 340	Ala	Glu	G1u	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe		
Leu	Glu	Gly 355	Lys	Met	Glu	Ile	Asp 360	Asp	Phe	Leu	Ser	Ser 365	Phe	Met	Glu		
Lys	Arg 370	Thr	He	Cys	His	Cys 375	Arg	Arg	Ala	Lys	G1u 380	Glu	Lys	Leu	Gln	·	•
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Val	Arg	Asn	Ser 20	Lys	Lys	Arg	Pro	Ala 25	Ser	Pro	Ser	His	Asn 30	Gly	Ser	
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Ser Gly Gly Gly Tyr Gly Ala Ser Lys Lys Lys Ala Ser Ala Ser
Ser Phe Ala Gln Gly Ile Ser Met Glu Ala Met Ser Glu Asn Lys Met
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Val Pro Ser Glu Phe Ser Thr Gly Pro Val Glu Lys Ala Ala Lys Pro
                   70
                                       75
Leu Pro Phe Lys Asp Pro Asn Phe Val His Ser Gly His Gly Gly Ala
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               85
Val Ala Gly Lys Lys Asn Arg Thr Trp Lys Asn Leu Lys Gln Ile Leu
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Ala Ser Glu Arg Ala Leu Pro Trp Gln Leu Asn Asp Pro Asn Tyr Phe
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Ser Ile Asp Ala Pro Pro Ser Phe Lys Pro Ala Lys Lys Tyr Ser Asp
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Phe Ser Thr Ile Glu Glu Phe Ser Tyr Ile Arg Arg Leu Pro Ser Asp
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_				-		_	_			cag Gln			-	-	528

		-	•			•			-	- /	•		att Ile 190	•		576
_		-	-		-	_		-		_		•	aga Arg		_	624
			-			-	_	_		_	-	_	aaa Lys		•	672
					-	_		-	-	-	_	-	aga Arg		•	720
		_		_		-	-		-	-		-	aag Lys	-	-	768
		_		_	-	-			-		_		gag G1u 270			816
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<210> 284

<211> 315

<212> PRT

<213> Homo sapiens

<400> 284

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Ala	Leu	Leu	G1n 20	Val	Asp	Ser	Gly	Ser 25	Gly	Ser	Asp	Ser	Glu 30	Pro	Gly
J	Gly	35	•	Ū			40		•			45	·		•
	Thr 50					55					60				
G1n 65	Gln	Gln	Ser	Glu	Ala 70	Asn	G1u	Leu	Arg	Asn 75	Leu	Ala	Phe	Lys	Lys 80
Пe	Pro	Gln	Lys	Ser 85	Ser	His	Ala	Val	Cys 90	Asn	Ala	Gln	His	Asp 95	Leu
Pro	Leu	Ser	Asn 100	Pro	Val	Gln	Lys	Asp 105	Ser	Arg	Glu	Glu	Asn 110	Trp	Gln
Glu	Trp	Arg 115	Gln	Arg	Asp	Glu	Gln 120	Leu	Thr	Ser	Glu	Met 125	Phe	Glu	Ąla
Asp	Leu 130	Glu	Lys	Ala	Leu	Leu 135	Leu	Ser	Lys	Leu	Glu 140	Tyr	Glu	Glu	His
145	Lys		-	•	150					155					160
Met	Asn	Lys	Lys	Asp 165	Lys	Arg	Lys	Asn	His 170	Gln	Gly	Lys	Asp	Arg 175	Pro
Leu	Thr	Val	Ser 180	Leu	Lys	Asp	Phe	His 185	Ser	Glu	Asp	His	Ile 190	Ser	Lys
	Thr	195					200	-				205			
Leu	G1u 210	Leu	Glu	Arg	Lys	Asp 215	Ala	Glu	IJе	Gln	Lys 220	Leu	Lys	Asn	Val
11e 225	Thr	Gln	Trp	Glu	Ala 230	Lys	Ţyr	Lys	Glu	Val 235	Lys	Ala	Arg	Asn	Ala 240
G1n	Leu	Leu	Lys	Met 245	Leu	Gln	Glu	Gly	G1u 250	Met	Lys	Asp	Lys	A1a 255	Glu
He	Leu	Leu	G1n 260	Val	Asp	Glu	Ser	G1n 265	Ser	Ile	Lys	Asn	G1u 270	Leu	Thr
Ile	Gln	Val 275	Thr	Ser	Leu	His	A1a 280	Ala	Leu	Glu	G1n	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	Glņ	Ala	G1u 295	Leu	Ala	Lys	Tyr	G1n 300	Gly	Gly	Arg	Lys
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<211> 1308

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	gac Asp 50		-				-				-	_		-	192	
	gcc Ala														240	
	tgg Trp				-	_	-						-	_	288	
	ctg Leu			_	_	_	 		His	-	-		_	-	336	
	atg Met														384	
	ata Ile 130			_								-			432	

ctt tgg aag cat ggg aat ctg cga aat gtg ctg atc ttg atg gat caa

Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	Gln 160	
														cga Arg 175		528
														cat His		576
														gct Ala	-	624
				-	-	_	_	_	-					ctg Leu		672
	_			-	-		-				_	-		gtg Val	_	720
						-	-	-	_	-	_		_	ttg Leu 255		768
						-	_	_					-	agg Arg		816
				_	-	_			_	-	_			ttc Phe		864
														cgt Arg		912
														tat Tyr		960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe	
	agg Arg			-											-	1056
	atc Ile											_				1104
	atc Ile 370															1152
	acc Thr															1200
_	ctc Leu		-		-		_	_	-		-	-	_	-	_	1248
-	gag G1u	-	-	-				_	-		-				-	1296
	cct Pro	_	taa *													1308
	<2 <2	210> 211> 212> 213>	435	o sap	oiens	5							•			
Mo+		100>		V-1	The	Clu	Lou	Tun	Dno	C1	Lou	Dho	Thn	Lou	Lou	
1	Gly			5					10					15		
Leu	Lys	Leu	Va1 20	Ser	Cys	Thr	Leu	G1y 25	Gln	Lys	Met	Pro	Thr 30	Cys	Pro	
Trp	Ser	His 35	Arg	Arg <sub>.</sub>	His	Val	Met 40	Gln	Gln	G1y	Glu	G1n 45	Gln	Gln	Ile	

Pro	Asp 50	Pro	Cys	Arg	Leu	Ser 55	Thr	Ala	Thr	Leu	Lys 60	Cys	Leu	Gln	Ala
G1n 65	Ala	Met	Arg	Glu	Gly 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asn 80
Leu	Trp	Thr	Leu	Leu 85	Ser	Ser	Pro	Ser	Thr 90	His	His	Ile	Gly	Va1 95	Cys
Ser	Leu	Ala	Arg 100	Ser	Met	Ala	Val	Trp 105	Gln	His	Gly	Val	Ile 110	Leu	Asp
Ile	Met	Glu 115	Gln	Leu	Leu	Ser	Ser 120	Leu	Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr
Arg	Ile 130	Thr	Gly	Ala	Ala	Phe 135	Phe	Ser	Glu	Leu	Met 140	Lys	Glu	Pro	He
Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	Gln 160
Ser	Ala	Trp	Asp	Ser 165	Asn	Ala	Thr	Leu	Arg 170	Gln	Met	Ala	Ile	Arg 175	Gly
Leu	Gly	Asn	Thr 180	Ala	Ser	Gly	Ala	Pro 185	His	Lys	Val	Lys	Lys 190	His	Lys
G1n	Leu	Met 195	Leu	Glu	Şer	Ile	Ile 200	Arg	Gly	Leu	Tyr	His 205	Leu	Ala	Arg
Thr	Glu 210	Val	Val	Cys	Glu	Ser 215	Leu	Lys	Ala	Leu	Lys 220	Lys	Ile	Leu	Glu
Leu 225	Leu	Thr	Asp	Arg	Asp 230	Val	Ser	Phe	Tyr	Phe 235	Lys	Glu	Ile	Val	Leu 240
Gln	Thr	Arg	Thr	Phe 245	Phe	Glu	Asp	Glu	G1n 250	Asp	Asp	Val	Arg	Leu 255	Thr
			260			·		265	•				Arg 270		
Lys	Пe	Phe 275	Phe	Ala	Glu	Glu	Ile 280	Lys	Lys	Ser	Leu	Ile 285	Ser	Phe	Leu
Leu	His 290	Leu	Trp	Asp	Pro	Asn 295	Pro	Lys	Ile	Gly	Val 300	Ala	Cys	Arg	Asp
Va1 305	Leu	Met	Val	-	Ile 310		Phe			Leu 315		Glu	Leu	Tyr	Gly 320
Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	Ala 345	Lys	Lys	Asn	Gln	G1u 350	Ile	Leu
Trp	Ile	Leu 355	His	Thr	His	Ser	Phe 360	Thr	Phe	Phe	Thr	Ser 365	Thr	Trp	Glu
Val	Ile 370	Arg	Ser	Ala	Ala	Va1 375	Lys	Leu	Thr	Asp	A1a 380	Val	Val	Leu	Asn
Leu 385	Thr	Ser	Gln	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395	Glu	Gln	Leu	Thr	Thr 400

Arg	Leu	Gln	Ala	Leu 405	Arg	Gln	Asp	Pro	Cys 410	Ile	Ser	Val	Gln	Arg 415	Ala	
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					gca Ala		-	-			-	-			_	144
					ctg Leu	-						-				192
_	-				gtg Val 70	_	-		_				_	_	-	. 240
	_	-	_		ttc Phe			-	-	_		-	-		_	288
					aag Lys											336

	-	-	_	_	-	gtg Val		-	_		-	_		_		384
_						ctt Leu 135				_	-				_	432
		_	_	-	-	aag Lys							_		•	480
		-		-	_	cag Gln				_	-	_	•	_	•	528
	-	-				ctg Leu			Thr				-			576
	_			_		agg Arg		_					_		•	624
						atg Met 215										672
_				_	-	tgc Cys	_		_	-			-			720
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tca	_															822

425

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WO 01/29221

426

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_	atc Ile				-	_		_		_	-	-	_	-		144
	gaa Glu 50	-	_		-		-	_				-	-	_	gca. Ala	192
_	gtt Val	-		-		_	-							-	_	240
	gtt Val				Пe		His	۷a٦	Lys		Glu	Arg	Pro			288
	cca Pro															336
-	aag Lys			-	-	_					-			_	-	384
ttt	aaa	caa	cag	ctg	aaa	gaa	cta	aag	aag	caa	tgt	ggt	ctt	caa	gct	432

PCT/US00/29052

Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	G1n	Cys 140	Gly	Leu	Gln	Ala	
						aca Thr										480
		_	-			ttc Phe		_				_		_	_	528
	_		-			aaa Lys								:		576
-		-	-	-		gag G1u								-	_	624
	_					tgt Cys 215	_		_	-		_	-		_	672
		-	_	-	-	ctt Leu									_	720
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1 Phe	Ser	Gly		5 Glu	Ser	Ala	Leu		10 Ser	Leu	Lys	Asn		15 Gln	Ala	
Cys	Пе	Asn 35	20 Ser	Gly	Met	Asp	Thr 40	25 Ala	Ser	Ser	Val	Ala 45	30 Leu	Asp	Leu	

Val	Glu 50	Ser	Gln	Thr	Glu	Va1 55	Ser	Ser	Glu	Tyr	Ser 60	Met	Asp	Lys	Ala	
Met 65	۷a۱.	Glu	Phe	Ala	Thr 70	Leu	Asp	Arg	Gln	Leu 75	Asn	His	Tyr	Val	Lys 80	
Ala	Val	Gln	Ser	Thr 85	He	Asn	His	Val	Lys 90	Glu	Glu	Arg	Pro	G1u 95	Lys	
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Phe	Lys 130	Gln	G1n	Leu	Lys	G1u 135	Leu	Lys	Lys	Gln	Cys 140	Gly	Leu	Gln	Ala	
Asp 145	Arg	G1u	Ala	Asp	Gly 150	Thr	Glu	Gly	Val	Asp 155	Glu	Asp	Ile	Ile	Val 160	
Thr	Gln	Ser	Gln	Thr 165	Asn	Phe	Thr	Cys	Pro 170	Ile	Thr	Lys	Glu	Glu 175	Met	
Lys	Lys	Pro	Val 180	Lys	Asn	Lys	Val	Cys 185	Gly	His	Thr	Tyr	Glu 190	Glu	Asp	
Ala	Пe	Val 195	Arg	Met	Ile	Glu	Ser 200	Arg	Gln	Lys	Arg	Lys 205	Lys	Lys	Ala	-
Tyr	Cys 210	Pro	Gln	Ile	Gly	Cys 215	Ser	His	Thr	Asp	Ile 220	Arg	Lys	Ser	Asp	
Leu 225	Ile	Gln	Asp	Glu	A1a 230	Leu	Arg	Arg	Ala	Ile 235	Glu	Asn	His	Asn	Lys 240	
Lys	Arg	His	Arg	His 245	Ser	Glu					٠					
		210>				•										
		211> 212>											•			
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		220>														
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				A,T,	957) .C or	G										
		100>														
				-	999 Gly										_	48
7				9					TO					10		

-	-			-	_	-				-				acc Thr			96
-		_	_		-	-		_			-		_	ctc Leu	-		144
	_	-	_	_	-		-	_		-	_	_	-	gac Asp			192
-	-					_			-		_	_		ctg Leu	_		240
		-		-	-		_					_		ctc Leu 95		2	288
_	_				_	-	-		_				-	cca Pro		(	336
	-		-	-	-				-	-			-	gtg Val		Ć	384
		_	_	-			_	-			_		_	atc Ile		4	432
														atc Ile		4	480
														gac Asp 175	· .	Ę	528
														cac His	-	Ę	576

_	_		_	-		-		-		-			-	ctg Leu	_	624
_	_				-	-	_					•	•	ttc Phe	•	672
		•	_			-	-	_						ctc Leu		720
		_	_		_	-					-	-	_	ggc Gly 255	-	768
	_			Cys	_				_	_	_			aac Asn	•	816
														tcg Ser		864
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<211> 318

<212> PRT

<213> Homo sapiens

<220>

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315

310

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							_	gta Val	_	_	_		-		-	192	
		-	-	_	-	-		tac Tyr	-			 -	_	-	Ž	240	
								tgg Trp							ž	288	
								aga Arg 105							(	336	
								gag Glu							Ç	384	
								agt Ser							2	432	

			gct Ala							480
			atg Met							528
			cac His							576
			ctg Leu							624
			ttc Phe 215							672
			atg Met			_	-		-	720
			gcc Ala							768
			att Ile							816
			ctt Leu							864
			aga Arg 295							912
			gac Asp		Lys					960

434

	_			_	cac His		-	-	•	•	•	_	-		•	1008
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-	_	-	-		gtc Val	_								-		1104
tga *													•			1107

<210> 294

<211> 368

<212> PRT

<213> Homo sapiens

<400> 294

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				165					170					175			
Val	Tyr	Asp	Gln 180	Pro	Phe	His	Ser	Ser 185	Ala	Leu	Glu	Lys	Glu 190	Glu	Ala		
Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu		
Ser	G1u 210	Lys	Ala	Lys	Glu	Phe 215	Leu	Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe		
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235	Leu	Ser	Leu	Ala	Asn 240		
Gln	Pro	Val	Ile	His 245	Ser	Ala	Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255	Lys		
Asp	Thr	Thr	Ser 260	Lys	Ala	Пe	His	Ser 265	Ile	Phe	Lys	Asn	Ala 270	Пe	Gln		
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Val 280	Phe	Gln	Lys	Asp	Asp 285	Gly	Phe	Asp	,	
	290					295					300	His					
305					310	·				315		His			320		
				325					330			Leu		335			
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-		-	_	-	_	_		-		-		cgc Arg		_			96

436

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									gaa Glu					192
Ser				_			-		cgg Arg			•		240
									agg Arg	-	_			288
									agc Ser					336
		_	_	-			_		gac Asp 125		_		,	384
	-	-				_		-	gac Asp	_	_			432
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<210> 296

<211> 185

<212> PRT

437

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<213> Homo sapiens
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Val Ser Asn Asp Pro Asp Val Ile Lys Leu Gln Glu Ile Pro Thr Phe

48

20 25 30 cag ccc ctt ttg aaa ggg cta ttg agt ggc cag act tcc cca aca aat 144 Gln Pro Leu Leu Lys Gly Leu Leu Ser Gly Gln Thr Ser Pro Thr Asn 35 40 gcc aaa ttg gag aaa ctg gac tct cag cag gtg ttg cag ctc tgc ctc 192 Ala Lys Leu Glu Lys Leu Asp Ser Gln Gln Val Leu Gln Leu Cys Leu 50 55 60 cga tat caa gat cac ctg cat cag tgt gca gag gcc gtt gct ttt gac 240 Arg Tyr Gln Asp His Leu His Gln Cys Ala Glu Ala Val Ala Phe Asp 65 70 75 cag aat get ttg gtt aaa ega ate aaa gag atg gat etg tet gta gaa 288 Gln Asn Ala Leu Val Lys Arg Ile Lys Glu Met Asp Leu Ser Val Glu 85 act ctg ttc agc ttc atg cag gag cgc cag aaa aga tac gcc aag tat 336 Thr Leu Phe Ser Phe Met Gln Glu Arg Gln Lys Arg Tyr Ala Lys Tyr 100 105 gcc gag cag atc cag aaa gtg aac gag atg tcc gcc atc ctc cgc cgc 384 Ala Glu Gln Ile Gln Lys Val Asn Glu Met Ser Ala Ile Leu Arg Arg 115 120 125 ata cag atg ggc atc gac cag act gtg ccc ctg ctg gac agg ctc aac 432 Ile Gln Met Gly Ile Asp Gln Thr Val Pro Leu Leu Asp Arg Leu Asn 130 135 140 age atg etg eec gag gge gag egg etg gag eec tte age atg aag eec 480 Ser Met Leu Pro Glu Gly Glu Arg Leu Glu Pro Phe Ser Met Lys Pro 145 150 155 160 gac cgc gag ctc agg ctg tag 501 Asp Arg Glu Leu Arg Leu \* 165

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<213> Homo sapiens

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Gln	Pro	Leu 35	Leu	Lys	Gly	Leu	Leu 40	Ser	Gly	Gln	Thr	Ser 45	Pro	Thr	Asn		
Ala	Lys 50	Leu	Glu	Lys	Leu	Asp 55	Ser	Gln	Gln	Val	Leu 60	Gln	Leu	Cys	Leu		
Arg 65	Tyr	Gln	Asp	His	Leu 70	His	Gln	Cys	Ala	G1u 75	Ala	Val	Ala	Phe	Asp 80		
	Asn			85	_	_			90		•			95			
Thr	Leu	Phe	Ser 100	Phe	Met	Gln	Glu	Arg 105	Gln	Lys	Arg	Tyr	Ala 110	Lys	Tyr		
Ala	Glu	G1n 115	Ile	Gln	Lys	Val	Asn 120	Glu	Met	Ser	Ala	Ile 125	Leu	Arg	Arg		
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-	cac His 50		-			-							-	-	_	1	.92
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	gtt Val		_							_				_	-	2	88
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	aaa Lys		_		_										-	5	28
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	gca Ala															6	24

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			aca Thr													720
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	tat Tyr		tga *													828
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l Leu	Ala	Ala	Asp 20	5 Pro	Leu	Asn	Arg	Arg 25	10 Ala	Пe	Val	Gln	Asp 30	15 Gln	Gly	
Cys		Pro 35	Gly	Leu	Пe	Leu	Phe 40		Asp	His	Pro	Asn 45		Pro	Val	
/al			Ala	Leu	Leu	A1 a 55		Arg	Tyr	Leu	Ala 60		Cys	Arg	Ala	
Asn 55	Arg	Glu	Lys	Met	Lys 70	Gly	Glu	Leu		Met 75	Met	Leu	Ser	Leu	Gln 80	

Asn	Val	He	Gln	Lys 85	Thr	Thr	Thr	Pro	G1y 90	Glu	Thr	Lys	Leu	Leu 95	Ala	
Ser	Glu	Пe	Tyr 100	Asp	Пe	Leu	Gln	Ser 105	Ser	Asn	Met	Ala	Asp 110	Gly	Asp	
Ser	Phe	Asn 115		Met	Asn	Ser	Arg 120	Arg	Arg	Lys	Ala	Xaa 125		Phe	Leu	
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Пe	Lys	Gly	۷a٦	Ile 165	Ser	Phe	Thr	Phe	Gln 170	Met	Ala	Val	Gln	Arg 175	Cys	
Val	·Val	Arg	Ile 180	Arg	Ser	Asp	Leu	Lys 185	Ala	Glu	Ala	Leu	Ala 190	Ser	Ala	
Пe	Ala	Ser 195	Thr	Lys	Val	Met	Lys 200	Ala	Gln	Gln	Val	Va1 205	Lys	Ser	Glu	
Ser	Gly 210	Glu	Glu	Met	Leu	Val 215	Pro	Phe	Gln	Asp	Thr 220	Pro	Val	Glu	Val	
G1u 225	Gln	Asn	Thr	Glu	Leu 230	Pro	Asp	Tyr	Leu	Pro 235	Glu	Asp	Glu	Ser	Pro 240	
Thr	Lys	Glu	Gln	Asp 245	Lys	Ala	Val	Ser	Arg 250	Val	Gly	Ser	His	Pro 255	Glu	
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		·00>													,	
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met 1	AId	ser	Ald	vai 5	Leu	ser	ser	val	Pro 10	ınr	ınr	Ala	ser	Arg 15	rne	

-					-	_	-				-		gaa G1u 30			96
	-			_				-					gga Gly	_	•	144
							-				_		aag Lys	-	-	192
_		_	_	-	-							-	ttt Phe	_		240
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	_				_	-	_	_		_	-	-	aat Asn 110			336
				_									ttt Phe			384
-			-	-	-			_			-		gaa Glu			432
	_	-		_	-	•	_					_	tcc Ser		_	480
-				-									gac Asp			528
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_			-	_	_			-					_	gga Gly		624
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	_		-	-			-					-		tgt Cys		720
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•		•		-		•			-	-	•		_	aag Lys	_	816
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Lys	Asn	Val 275	Ile	Thr	Gln	Trp	G1u 280	Ala	Lys	Tyr	Lys	G1u 285	Val	Lys	Ala	
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G1u	Leu	Thr	Пe	G1n 325	Val	Thr	Ser	Leu	His 330	Ala	Ala	Leu	Glu	G1n 335	Glü	
Arg	Ser	Lys	Val 340	Lys	Val	Leu	Gln	A1a 345	Glu	Leu	Ala	Lys	Tyr 350	Gln	Gly	
Gly	Arg	Lys 355	Gly	Lys	Arg	Asn	Ser 3 <u>6</u> 0	Glu	Ser	Asp	Gln	Cys 365	Arg			
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	_						-	_	_		_			ttg Leu		144
									_	-		_		ctg Leu		192
-	999 Gly		-				-					_		cag Gln		240

65					70					75					80	
-				-	-	aaa Lys										288
						tgt Cys										336
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-			-			aaa Lys 215	_	-	-					-	_	672
-			_	-	_	act Thr	-	_			_			-	_	720
	-	-	_			aga Arg	_						_			768

448

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235

Phe Glu Asp Lys Trp Phe Arg Lys Ile Lys Asp His Phe Cys Pro Phe

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		cag Gln 35													_	144
_	-	gga Gly	-			_			-	-						192
		gac Asp														240
		caa Gln		_		-	-								-	288
		cat His			_		_			-,		-			_	336
		gca Ala					-	-						-	_	<sup>-</sup> 384

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		ctg atc aaa Leu Ile Lys				-
Ala Cys T		cat cag aac His Gln Asn 200	Lys Ile	Ile Leu (		_
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-	_			-	att Ile	_	-	-		-	_	-		-		192
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	_				gac Asp	_		_				_	_			288
		_	_	_	ctg Leu			_				-		_		336
-	_	-		-	gtg Val	_	_	-	_		_	-				384
					cag Gln				_				_			432
					ggc Gly 150	_		_				_		_	_	480
					cag Gln	-				-	-	-		-		528

				165			•		170					175		
-														aaa Lys		576
_				_	_	-		_						aag Lys		624
_			-										-	cct Pro		672
-	_	_	_	_		Leu	_						-	gaa G1u	_	720
														gaa Glu 255		768
-				_	_	-						-		aag Lys	-	816
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Lys	Thr	A1a 35		Leu	Asp	Tyr	Ile 40		Arg	Cys	Arg	Pro 45		Asp	Ser	
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Gly 65	Glu	Asn	His	Glu	A1 a 70	Ala	Ala	Arg	Ile	G1n 75	Leu	Lys	Leu	Ile	Glu 80	
Ser	Gln	Pro	Trp	Glu 85	Asp	Ser	Leu	Lys	Asp 90	Gly	His	G1n	Leu	Lys 95	Gln	
Leu	Leu	Leu	Lys 100	Ala	Leu	Thr	Leu	Met 105	Leu	Asp	Ala	Ala	Glu 110	Ser	Tyr	
Ala	Lys	Asp 115	Ser	Cys	Val	Arg	Gln 120	Ala	Gln	His	Cys	Gln 125	Arg	Leu	Thr	
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Ser	Ile 210	Phe	Glu	Glu	Ile	Ser 215	Lys	Lys	Tyr	Lys	G1n 220	His	Gln	Pro	Thr	
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Gln	Leu	Tyr 35		Ser	Leu	Met	Ala 40		His	Ala	Ser	Arg 45		Arg	Val	
Ile	Lys 50		Cys	Пe	Ala	G1n 55	-	Ser	Ala	Val	Va1 60	. –	Asn	Leu	Arg	
Glu	Glu	Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	Gln	Leu	

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Glu	Glu	Val	Val 100	85 Asn	Asp	Arg	Ser	Trp 105	90 Lys	Val	Phe	Asn	Glu 110	95 Arg	Cys	*
Arg	Ile	His 115	Phe	Lys	Pro	Pro	Lys 120	Asn	Glui							
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						ggt Gly 55										192
					-	atg Met	-	-	-	-		_	_			240
						gcc Ala	-	_						-		288
						gag Glu										336

			100					105					110				
	aat Asn									• •		_		-			384
	cat His 130																432
	tcg Ser	-			-			-	_			_		-	_		480
	cta Leu			_		-				_		-					528
-	cac His	_		_		tga *					·						549
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Gly	Pro	Arg	Ala 20	Ala	Gly	Ala	Gln	G1y 25	Leu	Thr	Gln	Thr	Pro 30	Thr	Glu		
Met	Gln	Arg 35		Ser	Leu	Arg	Phe 40		Gly	Pro	Met	Thr 45		Ser	Tyr	· ·	
Arg	Ser 50		Ala	Arg	Thr	Gly 55		Pro	Arg	Lys	Thr 60		Ile	Пe	Leu		
	Asp	Glu	Asn	Asp	Ala 70		Ala	Asp	Ala	Asp 75		Leu	Ala	Gly			
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Ser	Ser	Ala	Ile 100		Glu	Glu	Asp	Gly 105		Ser	Glu	Glu	Gly 110	95 Val	Val		
Пe	Asn	Ala		Ala	Leu	Gly	Pro		Ala	Leu	Pro	Leu		Val	Gly		

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His	His 130	Glu	Pro	Glu	Pro	Va1 135	Trp	Glu	Ala	Ala	Arg 140		Phe	Arg	Ala	
Pro 145	Ser	Ser	Trp	Gly	Ala 150	Glu	Pro	Ala	Pro	His 155	Gly	Ala	Gln	Ala	Leu 160	
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Gly	Leu	Pro	G1y 20	Ala	Trp	Gly	Lys	Leu 25	Ala	Thr	Phe	Asn	Ser 30	Trp.	Tyr	٠
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Leu	rne	35	Set.	VdI	Ald	rne	40	ASII	Ald	ASP	Ala	45	Arg	Arg	m	
tgc	cca	cag	ctc	acc	acc	tat	gga	tgc	cat	ggc	tct	ggg	caq	ctt	tca	192
								_			Ser 60		-			
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Lys 65	Gln	Val	Pro	Val	Val 70	Ser	Ser	Ala	Val	*						

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Leu Phe Asn Ser Val Ala Phe Gln Asn Ala Asp Ala Thr Arg Arg Thr
Cys Pro Gln Leu Thr Thr Tyr Gly Cys His Gly Ser Gly Gln Leu Ser
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Lys Gln Val Pro Val Val Ser Ser Ala Val
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                 5
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                                     10
                                                          15
ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
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gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
                                                                      144
Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
         35
                             40
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	cta Leu 50															192
	cga Arg												_		_	240
	gag Glu			_	-	-							_	-		288
	aag Lys	-		-	-		_	_						_	•	336
-	gat Asp		_			_			_	_			_		000	384
	tgg Trp 130	_				-					_	-		_		432
	ccc Pro												-	_	-	480
	tgc Cys															528
	ggc Gly															576
	ggc Gly							_						_	-	624
	agg Arg 210															672

		_	gcc Ala		_				-	-	-		-	720
			tac Tyr 245											768
-		-	ggc Gly			-			_				_	816
-	•		agc Ser		_	-	_	_		-			gag Glu	864
			gat Asp		-							_	_	912
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Pro	Leu	Trp	Ser 20	Ser	Ser	Leu	Pro	G1y 25	Leu	Asp	Thr	Ala	Glu 30	Ser	Lys
Ala	Thr	Ile 35	Ala	Asp	Leu	Ile	Leu 40	Ser	Ala	Leu	Glu	Arg 45	Ala	Thr	Val
Phe	Leu 50	Glu	Gln	Arg	Leu	Pro 55	Glu	Ile	Asn	Leu	Asp 60	Gly	Met	Val	Gly
Va1 65	Arg	Val	Leu	G1u	G1u 70	Gln	Leu	Lys	Ser	Va1 75	Arg	Glu	Lys	Trp	A1a 80
	•			85	Gln				90					95	-
	-		100		Ala			105					110	•	
		115			Leu		120					125			
	130				His	135	·				140				
145					Pro 150					155			_		160
				165	Leu				170		·			175	
	_		180	·	Leu	•		185					190	-	_
		195			Ser		200					205	·		_
	210				Gln	215					220		·	-	
225			•		Asn 230			•		235		_			240
				245	Pro.		_	·	250					255	
			260		Gly			265					270		
		275			Trp		280				·	285		•	
	290				Glu	295		,			300				
His 305	Phe	Ser	Arg	Arg	Va1 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	G1'y 320
-				325.					330				-	335	
Leu	Tyr	Ile	Leu 340	Ala	Glu	Tyr	Pro	Pro 345	Ala	Asn	Arg	Glu	Pro 350	His	Pro

Ser	Thr	Pro 355	Pro	Pro	Pro	Ser	Ser 360	Arg							
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					_				-	-		gag Glu			192
				_	-				-			cga Arg	-	_	240
												gcc Ala			288
												gct Ala 110			336

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	_	_			aac Asn		-	-			_	_		_		432
				-	atg Met 150		_					_			_	480
					gag Glu					Leu						528
	_	Leu	-	-	atg Met	_										576
	-		-		cct Pro		_	-		-		_				624
		_	-	_	cag Gln									_	_	672
_	_		-		gga Gly 230	-	-	-					-		_	720
					ggc Gly											768
-		_	_		gac Asp	-		_					_			816
_		_			ctg Leu								_			864

				_		cag G1n 295						-	_			912
-	_		-		-	ttc Phe	-			_			-	_		960
	-	-	_	-	-	ctg Leu							-	_	_	1008
			_	-		gcc Ala					_	_			_	1056
	_		-	-	_	gaa Glu		_	_			-	-	_		1104
_						agc Ser 375	_	_		-	-	_				1152
			-			ctg Leu		_	-	_					~ ~	1200
	_			-		cta Leu				-				_	•	1248
						999 Gly										1296
						ggt Gly										1344
Gly					Leu	atc Ile 455										1392

gcc agc ctt ttc ggc ctc tac ttc cac cag cac ttg gca ggc tcc tag 1440 Ala Ser Leu Phe Gly Leu Tyr Phe His Gln His Leu Ala Gly Ser \* 465 470 475 <210> 318 <211> 479 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(479) <223> Xaa = Any Amino Acid <400> 318 Met Ala Val Leu Gly Val Gln Leu Val Val Thr Leu Leu Thr Ala Thr Leu Met His Arg Leu Ala Pro His Cys Ser Phe Ala Arg Trp Leu Leu 25 Cys Asn Gly Ser Leu Phe Arg Tyr Lys His Pro Ser Glu Glu Glu Leu Arg Ala Leu Ala Gly Lys Pro Arg Pro Arg Gly Arg Lys Glu Arg Trp 55 Ala Asn Gly Leu Ser Glu Glu Lys Pro Leu Ser Val Pro Arg Asp Ala Pro Phe Gln Leu Glu Thr Cys Pro Leu Thr Thr Val Asp Ala Leu Val . 90 Leu Arg Phe Phe Leu Glu Tyr Gln Trp Phe Val Asp Phe Ala Val Tyr 105 Ser Gly Gly Val Tyr Leu Phe Thr Glu Ala Tyr Tyr Tyr Met Leu Gly 120 125 115 Pro Ala Lys Glu Thr Asn Ile Ala Val Phe Trp Cys Leu Leu Thr Val 130 135 140 Thr Phe Ser Ile Lys Met Phe Leu Thr Val Thr Arg Leu Tyr Phe Ser 150 155 Ala Glu Glu Gly Gly Glu Arg Ser Val Cys Leu Thr Phe Ala Phe Leu 165 170 Phe Leu Leu Leu Ala Met Leu Val Gln Val Val Arg Glu Glu Thr Leu 180 185 Glu Leu Glý Leu Glu Pro Gly Leu Ala Ser Met Thr Gln Asn Leu Glu 200

Pro Leu Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys

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		He	Arg	Val	•			Val	۷al	Gly		Val	Leu	Gly	
225	Lau	The	Dha	Daa	230	1	A	1	۸٦	235	Th	114 -	A	A	240
				245					250				Arg	255	
Leu	Thr	Met	Ser 260	Glu	Asp	Arg	Pro	Met 265	Leu		Phe	Leu	Leu 270	His	Thr
Ser	Phe	Leu 275	Ser	Pro	Leu	Phe	Ile 280	Leu	Trp	Leu	Trp	Thr 285	Lys	Pro	Ile
Ala	Arg <sup>-</sup> 290		Phe	Leu	His	G1n 295		Pro	Phe	Gly	G1u 300		Arg	Phe	Ser
Leu 305	Ĺeu	Ser	Asp	Ser	Ala 310	Phe	Asp	Ser	Gly	Arg 315	Leu	Trp	Leu	Leu	Val 320
Val	Leu	Cys	Leu	Leu 325	Arg	Leu	Ala	Val	Thr 330	Arg	Pro	His	Leu	G1n 335	Ala
Tyr	Leu	Cys	Leu 340	Ala	Lys	Ala	Arg	Val 345	Glu	Gln	Leu	Arg	Arg 350		Ala
Gly	Arg	11e 355	Glu	Ala	Arg	G1u	Ile 360	Gln	Gln	Arg	Val	Val 365	Arg	Val	Tyr
Cys	Tyr 370	Val	Thr	Val	Val	Ser 375		G1n	Tyr	Leu	Thr 380		Leu	Пе	Leu
Thr 385	Leu	Asn	Cys	Thr	Leu 390		Leu	Lys	Thr	Leu 395		Gly	Tyr	Ser	Trp 400
Gly	Leu	Gly	Pro	Ala 405	Pro	Leu	Leu	Ser	Pro 410	Asp	Pro	Ser	Ser	Ala 415	Ser
Ala	Ala	Pro	Ile 420	Gly	Ser	Gly	Glu	Asp 425	Glu	Val	Xaa	Gln	Thr 430	Ala	Ala
Arg	Ile	A1a 435	Gly	Ala	Leu	Gly	Gly 440	Leu	Leu	Thr	Pro	Leu 445	Phe	Leu	Arg
Gly	Val 450	Leu	Ala	Tyr	Leu	Ile 455	Trp	Trp	Thr	Ala	Ala 460	Cys	Gln	Leu	Leu <sub>.</sub>
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														cca Pro		96
	_								-			_		gaa Glu	•	144
			-			-	_		_		-			gtg Val	•	192
														atg Met		240
														cgg Arg 95		288
	ccc Pro			_	_	_								tga *		333
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Ser	Va1	Thr	G1y 20	Ser	Gly	Phe	Ser	Va1 25	Ser	Asp	Leu	Ala	Pro 30	Pro	Arg	
Lys		Leu 35	Phe	Thr	Tyr		Lys 40	Gly	Ala	Gly	Glu	Met 45	Leu	Glu	Asp	
Gly			Arg	Phe	Leu			Ser	Val	Phe	Ser		Gln	Val	Ala	

Ser Thr Leu Lys Gln Val Lys His Asp Gln Gln Val Ala Arg Met Glu

65					70					75					80	
	Leu	Ala	Gly	Leu 85		Glu	Glu	Leu	G1u 90		Asp	Glu	Trp	Arg 95		
Lys	Pro	Ile	Glu 100		Leu	Leu	Gly	Phe 105		Pro	Ser	Ser	Gly 110	30		
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	_		-		-	_			_	_		cag Gln				96
									-			act Thr 45	-	_		144
											_	gtc Val				192
												agt Ser				240
												ttt Phe				288

					att Ile											336
					aaa Lys	-		_				-		_		384
-	_				cct Pṛo											432
	_				ttt Phe 150		-			-		-	_		•	480
				-	gca Ala	-					_	-	_		_	528
					cca Pro					-	_	-	_			576
_	_			-	ata Ile		-		_							624
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					ctt Leu 230								-	-		720
		_	-	_	gcc Ala	_		_		-		-				768
					gaa Glu									_		816

4.71

														gca Ala		864
_			-	-		_	-	-	-				_	cag Gln	•	912
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													_	aga Arg 335		1008
-		-		_	-		Ξ.	-			-			ctc Leu		1056
														ccg Pro	-	1104
		-		-					_		_			gtc Val		1152
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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
                        55
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
                    70
                                        75
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
                        135
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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                                        155
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Ala Leu Leu
                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
                                185
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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Lys 225	Ala	Ala	Ser	Pro	Leu 230	Gly	Ser	Pro	Glu	Leu 235	Cys	Pro	Ser	Ala	Leu 240
	Gly	Leu	Ser	G1n 245	Ala	Met	Lys	Leu	Pro 250		Pro	Ala	His	His 255	
Trp	Ser	Leu	Leu 260	_	Glu	Ala	Thr	Gly 265		Ile	Phe	Asp	Leu 270		Pro
Asn	Lys	I1e 275		Arg	Lys	Asp	Leu 280		Leu	Tyr	Пе	Ser 285		Ala	Lys
Cys	Leu 290		Glu	Met	Thr	Asp 295		Asp	Ala	Asn	Arg 300		Ala	Gln	Val
Thr 305		Ser	Asn	Ile	Glu 310		Ala	Ala	Phe	Val 315		Leu	Tyr	Leu	Va1 320
	Gln	Gly	Arg	Phe 325	Pro	Leu	Val	Asn	Leu 330		Asp	Met	Leu	Arg 335	
Ala	Thr	Ala	Val 340		Ala	Trp	Ala	Asp 345		Thr	Ala	Pro	Leu 350		Leu
Gly	Leu	Ser 355	Ala	Ser	Trp	Leu	Pro 360	Trp	His	Gln	Glu	Asn 365		Pro	Ala .
Gly	Pro 370	Val	Pro	Ser	Phe	Leu 375	Gly	Arg	Ser	Pro	Met 380	His	Arg	Val	Thr
Leu 385	Gln	Glu	۷a٦	Leu	Thr 390	Leu	Leu	Pro	Asn	Ser 395	Met	Ala	Leu	Leu	Leu 400
Gln	Lys	G1u	Pro	Trp 405	Lys	G1u	Gln	Thr	Gln 410	Lys	Phe	Ile	Asp	Trp 415	Leu
Phe	Ser	Ile	Met 420	Glu	Ser	Pro	Lys	G1u 425	Ala	Leu	Ser	Ala	G1n 430	Ser	Arg
Asp	Leu	Leu 435	Lys	Ala	Thr	Leu	Leu 440	Ser	Leu	Arg	Val	Leu 445		Glu	Phe
Lys	Lys 450	Lys	Ala	Val	Trp	Thr 455	Arg	Ala	Tyr	Gly	Trp 460				
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					tct Ser 70											240
•			-		agc Ser		_	Pro	-	_	-				_	288
_					att Ile								_			336
					aaa Lys	-		_				-		-		384
					cct Pro											432
	_				ttt Phe 150		_			-		_	_		•	480
	_			_	gca Ala	_			_		_	-	_		-	528

	-						-			-	_	_	ctg Leu 190			576
_	•			_			-		-				cac His			624
-	_	_		_			-				_		gca Ala	_		672
	-	_											agt Ser		tta Leu 240	. 720
													cac His			768
	_	_			_	-						_	ctc Leu 270	_		816
	_			_	_	-			-			-	ata Ile	_		864
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													tac Tyr			960
			_			_	_	Asn	-				ctg Leu			1008
-	-	-											att Ile 350			1056

						att Ile		-				-		-	_	11	L04
_	-	-				ttg Leu 375	_	_	-				-		_	11	.52
-		-				ttt Phe			_			-		-	_	12	200
_			-	_		ttt Phe			_		-	-		-	-	12	248
		-				ctc Leu			-	_	_		_			12	296
	-	-				gct Ala					-					13	344
		-			_	act Thr 455	-			-						13	92
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				-		cta Leu						-			-	14	88
						agg Arg										15	36
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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
                                    90
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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                            120
                                                125
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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                                        155
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
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Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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His	Gly	Leu	Ser	G1n 245		Met	Lys	Leu	Pro 250			Ala	His	His 255	-
Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265	Lys	Ile	Phe	Asp	Leu 270		Pro
Asn	Lys	I1e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Ile	Ser 285	Ile	Ala	Lys
Cys	Leu 290	Leu	Glu	Met	Thr	Asp 295	Asp	Asp	Ala	Asn	Arg 300		Ala	Gln	Val
Thr 305		Ser	Asn	Пe	Glu 310	Lys	Ala	Ala	Phe	Val 315	Lys	Leu	Tyr	Leu	Val 320
Ser	G1n	Gly	Arg	Phe 325	Pro	Leu	Val	Asn	Leu 330	Thr	Asp	Met	Leu	Ser 335	Val
Ala	Val	Gln	His 340	Arg	Glu	Lys	Glu	Va1 345	Leu	Ala	Trp	Met	Ile 350	Leu	His
Ser	Leu	Tyr 355	Gln	Ala	Arg	Ile	Val 360	Ser	His	Ala	Asn	Thr 365	Gly	Val	Leu
Lys ·	Arg 370	Met	Glu	Trp	Leu	Leu 375	Glu	Leu	Met	Gly	Tyr 380	Пе	Arg	Asn	Val
A1a 385	Tyr	Gln	Ser	Thr	Ser 390	Phe	His	Asn	Thr	A1 a 395	Leu	Asp	Glu	Ala	Leu 400
Asp	Phe	Phe	Leu	Leu 405	Ile	Phe	Ala	Thr	Ala 410	Val	Val	Ala	Trp	Ala 415	Asp
His	Thr	Ala	Pro 420	Leu	Leu	Leu	Gly	Leu 425	Ser	Ala	Ser	Trp	Leu 430	Pro	Trp
His	Gln	G1u 435	Asn	Gly	Pro	Ala	Gly 440	Pro	Val	Pro	Ser	Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	G1n	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
465		Met			470					475		_			480
Gln	Lys	Phe	Пe	Asp 485	Trp	Leu	Phe	Ser	Ile 490	Met	Glu	Ser	Pro	Lys 495	Glu
Ala	Leu	Ser	Ala 500	Gln	Ser	Arg	Asp	Leu 505	Leu	Lys	Ala	Thr	Leu 510	Leu	Ser
Leu	Arg	Val 515	Leu	Pro	Glu	Phe	Lys 520	Lys	Lys	Ala	Val	Trp 525	Thr	Arg	Ala
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agc cga gaa Ser Arg Glu 50					192
cac tgg gac His Trp Asp 65			-	 	240
tgg tca gaa Trp Ser Glu		-		 	288
ttt ggc ccc Phe Gly Pro			Ser Val		336
gaa gcc cgc Glu Ala Arg 115		_		 _	384
ggg gcc acc Gly Ala Thr 130	-				432

480

_				_		_		_		_	-		-	ctg Leu		480
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					-	-						_	_	cgg Arg		576
						-								gag Glu		624
								ccg Pro			-	_	tga *			666
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	Val	Arg	G1y 20		Gly	Pro	Ser	Va1 25		Ser	Arg	Leu	G1n 30	Asp	Ala	
Ala	Val		Arg		Gly			Ser	Thr					Thr	Leu	
Ser	Arg 50						. •					. •	Glu	Tyr	Asp	
His 65		Asp	Ala	Ala	Ile 70		Gly	Phe	Arg	G1u 75		Glu	Lys	Ser	Arg 80	
	Ser	Glu	Ala	Ser 85		Ala	Пе	Leu	G1n 90		Val	Gln	Ala	Ala 95		
Phe	Gly	Pro	Gly 100		Thr	Leu	Leu	Ser 105		Val	His	Val	Leu 110	Asp	Leu	
Glu	Ala	Arg 115		Tyr	Ile	Lys	Pro 120		Val	Asp	Ser	Ile 125		Phe	Cys	
0.3		- I								_	_	~~~				

Gly Ala Thr Ile Ala Gly Leu Ser Leu Leu Ser Pro Ser Val Met Arg

	130					135					140					
	Val	His	Thr	Gln		Pro	Gly	Glu	Trp		Glu	Leu	Leu	Leu		
145 Pro	Glv	Ser	Leu	Tvr	150	Leu	Ara	Glv	Ser	155 Ala	Δra	Tvr	Δsn	Phe	160 Ser	
110	uij	JCI	LCu	165		LCu	/ " y	uly	170	Aiu	Ai 9	',	лэр	175	Jei	
His	Glu	Ile	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
Pro	Arg	Gly 195	Ąrg	Arg	He	Ser	Val 200	Пe	Cys	Arg	Ser	Leu 205	Pro	Glu	Gly	
Met	Gly 210	Pro	Gly	Glu	Ser	G1y 215	Gln	Pro	Pro	Pro	A1a 220	Cys				
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-	-					-			-					aag Lys	-	96
											-		-	cct Pro	-	144
														gaa Glu	-	192
													_	atg Met		240
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482

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ttg tag
Leu \*
294

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Ala Asp Ser Ser Ile Phe Asp Ser Lys Val Thr Glu Ile Ser Lys Glu 20 25 30

Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Glu Met Pro Gln 35 40 45

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 50 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 65 70 75 . 80

Ser Val Glu Glu Phe Glu Gly Leu Asp Ser Pro Glu Phe Glu Met Tyr 85 90 95

Leu

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ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg 96 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

483

20 25 30

tgg aag ata aac aac ctc att gcc tca gaa tcc tac tac acc tac gcc
Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala
35 40 45

tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg

Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met

50 55 - 60

240

ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 75 80

gaa gcc gtg gag aga cag ttg atg acc tga 270 Glu Ala Val Glu Arg Gln Leu Met Thr \*

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<400> 330

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1 5 10 15

Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg 20 25 30

Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 35 40 45

Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 50 55 60

Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 75 80

Glu Ala Val Glu Arg Gln Leu Met Thr 85

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484

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gat gaa gtc tgg gtg caa gta gca cct cag cga aat gca cag gat cag
Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln
65 70 75 80

cag ggt tct ttg taa 255 Gln Gly Ser Leu \*

<210> 332

<211> 84

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<213> Homo sapiens

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 25
 30

 Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35
 40
 45

 Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Ser Phe Ser Asp 50
 55
 60

 Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln

485

65 G1n	Gly	Ser	Leu		70				75	,				80	
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atg Met							gca Ala					-		_	96
gcc Ala															144
act Thr		_		-	-		-	_		-	-	_	_		192
aac Asn 65															240
tag *															243

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Ala	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	G1u 45		Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	Glu 60	Ala	Leu	Ser	Asn	
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Met 1 gct Ala gca	cct Pro gtt	gtg Val ctg Leu gca	gtc Val ggt Gly 20	Leu 5 gcc Ala atg	Ser tgt Cys agc	Gln gcc Ala aaa	Glu tca Ser	999 Gly 25	Glu 10 gat Asp	Ser ttc Phe	Val gct Ala gtg	tct Ser	yal gta val 30	Gly 15 cag Gln aga	Ala gaa Glu cta	
Met 1 gct Ala gca Ala	cct Pro gtt Val	gtg Val ctg Leu gca Ala 35	gtc Val ggt Gly 20 aaa Lys	Leu 5 gcc Ala atg Met tac	tgt Cys agc Ser	Gln gcc Ala aaa Lys	tca Ser gtt Val 40	999 Gly 25 999 Gly aaa	Glu 10 gat Asp aaa Lys	Ser ttc Phe gtt Val	yal gct Ala gtg Val	tct Ser ttc Phe 45	yal gta yal 30 ccg Pro	Gly 15 cag Gln aga Arg	Ala gaa Glu cta Leu	96

487

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Ala	Val	Leu	Gly 20	Ala	Cys	Ala	Ser	Gly 25	Asp	Phe	Ala	Ser	Val 30	Gln	Glu	
Ala	Met	A1 a 35	Lys	Met	Ser	Lys	Va1 40	Gly	Lys	Val	Val	Phe 45	Pro	Arg	Leu	
G1n	Asp 50	Lys	Lys	Tyr	Tyr	Asp 55	Lys	Lys	Tyr	Gln	Val 60	Phe	Leu	Lys	Leu	
Va1 65		His	Gln	Lys	G1u 70		Leu	Ala	Ile	Met 75		Asp	Asp			
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		100>														
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			-					gtg Val 25				-				96
								atc Ile								144
-								gac Asp			-			-		192
							_	ggt Gly	-			_	-			240

65					70	70 75								80			
	-	act Thr			_					-				•		288	3
		tta Leu	_								_				_	336	5
		cgg Arg 115					_	_		-				-	_	384	4
_	_	aaa Lys	_						_	-						432	2
_	-	gat Asp	-		-		-	_	_		-	-	-	· .		480	)
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	_	cct Pro										_				567	7
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Ile	Leu	Ala	Va1 20	Phe	Tyr	Pro	Phe	Va1 25	Asp	Leu	Пe	Asp	Asn 30	Phe	Asn		
Gln	Thr	His 35		Tyr	Ala	Pro	Phe 40		Пe	Пе	Gly	Leu 45		Leu	Ala		
Leu	Gly	Ile	Phe	Ser	Phe	Thr		Asp	Thr	Trp	Ser		Ser	Arg	Gly		

	50					55					60					
Asp 65	Thr	Ala	Glu	He	Leu 70	Gly	Ser	Gly	Ala	Gly 75	He	Ala	Cys	Gly	Ser 80	
His	Val	Thr	Tyr	Asn 85	Met	Gly	Leu	Val	Leu 90	Asp	Pro	Ser	Leu	Asp 95	Thr	
Leu	Pro	Leu	Ala 100	Gly	Pro	Pro	Ile	Thr 105	۷al	Thr	Leu	Phe	Gly 110	Lys	Ala	
Ile	Leu	Arg 115		Leu	Ile	Gly	Met 120	Val	Phe	Val	Leu	Ile 125		Arg	Asp	
Val	Met		Lys	He	Thr	Ile 135	Pro	Leu	Ala	Cys	Lys 140	Ile	Phe	Asn	Ile	
Pro 145	Ċys	Asp	Asp	Ile	Arg 150	Lys	Ala	Arg	Gln	His 155	Met	Glu	Val	Glu	Leu 160	
	Tyr	Arg	Tyr	Ile 165		Tyr	Gly	Met	Val 170		Phe	Ser	Ile	Thr 175		
Phe	Val		Tyr .180		Phe	Phe	Phe	Ile 185		Ile	Ser					
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						999 Gly										48
				_		gtc Val										96
						gcg Ala										144
						gtg Val 55										192

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                                25
Lys Val Pro Gln Arg Met Ala Ala Glu Gly Ala Pro Glu Asp Asp Gly
                            40
Gly Gly Gly Ala Pro Gly Val Trp Gly Ala Gly Ala Pro Ala Glu Gly
                        55
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Tyr Leu Thr Ile Leu
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                 5
                                     10
gcg ggg gct ccg tca tcc cct ggg gaa tgc ctc ggc ctg caa gac cgc
                                                                       96
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
             20
                                 25
                                                     30
ata ccg cat tgg aac agg gaa acc acc tac ttc agc acc tcc ctc agc
                                                                      144
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
         35
                             40
                                                 45
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aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg
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Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
     50
                         55
                                             60
cat tcg gga tat ggc tcc ctg gcc agc ttg tga
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His Ser Gly Tyr Gly Ser Leu Ala Ser Leu *
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Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
                                25
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu
65
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                                                                       48
Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu
1
                 5
                                     10
                                                         15
atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca
                                                                       96
Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr
             20
                                 25
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492

ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 45 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 55 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile \* 65 70 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 55 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 70 65 75 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg 48 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu

10

15

493

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				-		-		-		_		_	ccc Pro	]	144
				_			_	-		_		-	aac Asn	1	192
													act Thr	 2	240
-	gaa Glu	_	-	_	_			-			_	-		2	285
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 Met
 Thr
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 Lys
 Asp
 Cys
 Ser
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 Met
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 Ala
 Leu
 Ser
 Pro
 Cys
 Leu

 Gln
 Asp
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 Ser
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 Arg
 Pro
 Val
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 Ser
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 Arg
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494

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495

145 150 155

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90

Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 105

Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 115 120 125

Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 135

Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 145 150

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			-		-	gtc Val							96	
						agc Ser 40							144	
						atc Ile						-	192	
	_	-	,	_		atg Met	-	-	_	_			240	
			-			aag Lys					-	tga *	288	

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90

95

<210> 351

<211> 165

<212> DNA

<213> Homo sapiens

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      <222> (1)...(165)
      <400> 351
atg tgc tcc atc ccc cgg cat ctg ctg cca ttg gtc ctg cct gtt gcg
                                                                      48
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
1
                 5
                                     10
tta ctt ctc tgt gcc ctg gag ccc ctc aag cac aga ggc ctc gaa agg
                                                                      96
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
ttg atc aga cat cct cag cac ctg gag cgg ggc ctg gca cac aag acg
                                                                     144
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
         35
                             40
                                                 45
gca atg aac ggc caa ccc tag
                                                                     165
Ala Met Asn Gly Gln Pro *
     50
      <210> 352
      <211> 54
      <212> PRT
      <213> Homo sapiens
      <400> 352
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
. 1
                                    10
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
            20
                                25
                                                    30
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
                            40
Ala Met Asn Gly Gln Pro
    50
      <210> 353
      <211> 159
      <212> DNA
      <213> Homo sapiens
      <220>
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<221> CDS
      <222> (1)...(159)
      <400> 353
atg tgc ttg agg gtt ttc acc ctg gcc ctc agt tgc ctg tgc ggg
                                                                      48
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                                     10
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                      96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                 25
             20
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
                                                                     144
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
                             40
                                                 45
cgt gtc ggg ctt tga
                                                                     159
Arg Val Gly Leu *
     50
      <210> 354
      <211> 52
      <212> PRT
      <213> Homo sapiens
      <400> 354
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                                   10
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                25
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
       35
                            40
                                                45
Arg Val Gly Leu
    50
      <210> 355
      <211> 210
      <212> DNA
     <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(210)
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_	ggt		atg			-				-		_	-	caa Gln 15	_		48
					-			-				-		cca Pro			96
		-	-			-		_				-		ctt Leu			144
														cag Gln			192
	gaa Glu			-	tag *												210
	<2 <2	210> 211> 212> 213>	69	o sap	oiens	5											
	<4	100>	356														
Met 1	Gly	Ala	Met	Asn 5	His	Asp	Thr	Asn	Tyr 10	Ser	Phe	Gln	Val	Gln 15	Cys		
Gly	Leu	Ile	Val 20		Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His	•	
Phe	Met	Asp 35		Glu	Leu	Cys	Ser 40		Tyr	Trp	Thr	Lys 45		Leu	Leu		
Arg	Leu 50		Glu	Tyr	Thr	Glu 55		Lys	Lys	Asn	G1n 60	Asn	Ile	Gln	Lys		
Pro 65	Glu	Tyr	Ser	Glu							•						
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<212> DNA

<213> Homo sapiens

WO 01/29221

500

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      <221> misc feature
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      <400> 357
atg gtc ctg ccg gtg gca gcc tat ggn ctg atc ctg atg gcc atg ctg
                                                                       48
Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
1
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                       96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
             20
                                 25
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
                             40
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                                             60
                         55
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
                                                                      240
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
65
                     70
                                         75
                                                                      243
tga
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<210> 358
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<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(80)

<223> Xaa = Any Amino Acid

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Met 1	Val	Leu	Pro	Val 5	Ala	Ala	Tyr	Xaa	Leu 10	Ile	Leu	Met	Ala	Met 15	Leu	
Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Ala	Gly	Trp	Gly	A1a 30	Leu	Leu	
Phe	Thr	Leu 35	Ser	Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45	Ala	Gln	Pro	
Leu	Pro 50	His	Ala	Arg	Leu	Val 55	Ile	Met	Thr	Thr	Tyr 60	Tyr	Ala,	Ala	Gln	
Leu 65	Leu	Ile	Thr	Leu	Ser 70	Ala	Leu	Arg	Ser	Pro 75	Val	Pro	Lys	Thr	Asp 80	
	<2 <2	210> 211> 212> 213>	324 DNA	sar	oiens	5										
	<2	220> 221> 222>		(3	324)											
atg		100> agc		tgt	ggt	tcc	ctt	gtg	gcc	atg	agt	gtt	gtg	gtg	gga	48
Met 1	Lys	Ser	Thr	Cys 5	Gly	Ser	Leu	Val	Ala 10	Met	Ser	Val	Val	Val 15	Gly	
			_	-	_	_	_	ccg Pro 25							_	96
				-				gag Glu				-		_		144
-	_							ctt Leu					_	_		192
	-		-			-		agt Ser							-	240
aqt	taa	qca	gga	aga	ctc	att	cta	aqt	qta	qat	ggc	tct	ggg	ttt	tat	288

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Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                 85
                                     90
                                                         95
                                                                     324
gag agg gtg aaa tct ttg gtc gtt aaa caa ttc tag
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
                 5
1
                                   10
Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
                        55
                                            60
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
                    70
                                       75
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                                    90
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
      <210> 361
      <211> 252
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(252)
      <400> 361
atg gag gaa gga ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
                                                                      48
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                 5
                                     10
                                                         15
                                                                      96
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
```

503

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg	
-					-	_	-				cga Arg	-				144
					-					-	tta Leu 60			-	_	192
		-		-			-			_	aaa Lys					240
	aaa Lys		taa *													252

<210> 362

<211> 83

<212> PRT

<213> Homo sapiens

<400> 362

 Met Glu Glu Gly Gly Gly Gly Gly Val Arg
 Ser Leu Val Pro Gly Gly Gly Pro 1

 1
 5
 10
 15
 15

 Val Leu Leu Val Leu Cys Gly Leu Leu Glu Ala Ser Gly Gly Gly Gly Arg 20
 25
 25
 30
 30

 Ala Leu Pro Gln Leu Ser Asp Asp Jle Pro Phe Arg Val Asn Trp Pro 35
 40
 45
 45

 Gly Thr Glu Phe Ser Leu Pro 55
 Thr Thr Gly Val Leu Tyr Lys Glu Asp 60

 Asn Tyr Val Ile Met Thr Thr Ala His Lys Glu Lys Tyr Lys Lys Lys 80

<210> 363

Lys Lys Asn

<211> 459

<212> DNA

<213> Homo sapiens

504

<220> <221> CDS <222> (1)...(459) -<400> 363 atg gat gga aca caa cag cag att ttt aaa atg tta gca gag gta cta 48 Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu 1 5 10 15 gga gga atc aat tgt gta aaa gcc tcg gtt ctt acg cct tat tac cac 96 Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His 20 25 aaa gta gat ttt gag tgt atc ttg gat aaa aga aaa aaa cct ctt ccg 144 Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro 40 35 tat gga agc cat aat ata gca ttg gga caa cta cca gaa atg ccc tgg 192 Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp 50 55 60 gaa toa aat ato gaa ata gtt gga toa agg ctg coa coa ggg got gaa 240 Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu 65 70 agg att gct ttg gaa ttt ttg gat tca aaa gca ctt tgt aga aat atc 288 Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile 85 95 cct cac atg aaa gga aaa tct gct atg aaa aaa cga cat ttg gaa att 336 Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile 100 105 ctg ggg tat cgt gta att cag att tcc cag ttt gaa tgg aac tct atg 384 Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met 115 120 125 gca ctg tca aca aag gat gct cgg atg gac tac ctg aga gaa tgt ata 432 Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile 130 135 140 ttt gga gaa gtc aag tca tgt ttg tag 459 Phe Gly Glu Val Lys Ser Cys Leu \* 145 150

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<210> 364
      <211> 152
      <212> PRT
      <213> Homo sapiens
      <400> 364
Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu
                                    10
Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
                                25
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro
                            40
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
                                105
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
                                                125
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
                        135
                                            140
Phe Gly Glu Val Lys Ser Cys Leu
145
                    150
      <210> 365
      <211> 600
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(600)
      <400> 365
atg gtg tgg cgc cgg ctt ctg cgg aag agg tgg gtg ctc gcc ctg gtc
                                                                       48
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
1
                 5
                                     10
                                                         15
ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
                                                                       96
```

Phe	Gly	Leu	Ser 20	Leu	Val	Tyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	Glu	
						agg Arg										144
			-			gtg Val 55				_			-	_	_	192
						aac Asn									_	240
						tgc Cys	-			-	_	_	-			288
_	_		-		-	cct Pro	_	_	_	_		_	_	_	••	336
_					_	tgc Cys	_	_				-	_		•	384
						caa Gln 135										432
		_	_	Phe		aac Asn					-	_	_			480
			-	_		tgc Cys								-		528
						ccc Pro			Lys					-	-	576
cca	CCC	αаσ	ctc	ttc	CCC	act.	t.aa									600

507 .

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Pro Pro Glu Leu Phe Pro Ala *
        195
      <210> 366
      <211> 199
      <212> PRT
      <213> Homo sapiens
      <400> 366
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
                                    10
Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
                                25
Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                                105
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                            120
Cys Leu Gin Pro Asn Lys Gin Leu Leu Leu Glu Arg Phe Leu Asn Arg
                       135
                                            140
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
145
                    150
                                        155
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
                                    170
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
           180
                                185
                                                    190
Pro Pro Glu Leu Phe Pro Ala
       195
      <210> 367
      <211> 249
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
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<222> (1)...(249)

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<210> 368

<211> 82

<212> PRT

<213> Homo sapiens

<400> 368

 Met
 Ser
 Lys
 Tyr
 Lys
 His
 Lys
 Ser
 Ser
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Ile
 Ile</th

509

Ser Gly

<210> 369 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 369 atg gac ggc cgc ggg gct ttc tgg aca gtg gcc att ccc aga gcc agg 48 Met Asp Gly Arg Gly Ala Phe Trp Thr Val Ala Ile Pro Arg Ala Arg 1 5 10 15 cag gaa ggc ctc ggg agg ctg ggg ctc ccg ttc ccg gtg aag cgg acg 96 Gin Glu Gly Leu Gly Arg Leu Gly Leu Pro Phe Pro Val Lys Arg Thr 25 20 ccg cca gcg ccc cag aac cca gga gga agc aca cag gcc cca cag aga 144 Pro Pro Ala Pro Gln Asn Pro Gly Gly Ser Thr Gln Ala Pro Gln Arg 35 · 40 gtg gtt ggc aag agt cac tcg ggg att agg atg ccg gcc aaa tcg cgg 192 Val Val Gly Lys Ser His Ser Gly Ile Arg Met Pro Ala Lys Ser Arg 50 55 aat ttg agg ctg gaa tcc aag ctc aac agg act gct gtg tgt gaa gca 240 Asn Leu Arg Leu Glu Ser Lys Leu Asn Arg Thr Ala Val Cys Glu Ala 65 70 75 ctc aag agg gcc cct aca acc aac ctg cca gga gtc ggc tcc tqa 285 Leu Lys Arg Ala Pro Thr Thr Asn Leu Pro Gly Val Gly Ser \* 85 90

<210> 370

<211> 94

<212> PRT

<213> Homo sapiens

<400> 370

Met 1	Asp	Gly	Arg	Gly 5	Ala	Phe	Trp	Thr	Val 10	Ala	Пе	Pro	Arg	Ala 15	Arg	
G1n	Glu	Gly	Leu 20	Gly	Arg	Leu	Gly	Leu 25	Pro	Phe	Pro	۷a٦	Lys 30	Arg	Thr	
Pro	Pro	A1 a 35	Pro	Gln	Asn	Pro	Gly 40	Gly	Ser	Thr	Gln	Ala 45	Pro	Gln	Arg	
Val	Val 50	Gly	Lys	Ser	His	Ser 55	Gly	Ile	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
65		,			70	•				75			• .	Glu	A1a 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 90	Gly	Val	Gly	Ser			
	<2 <2	210> 211> 212> 213>	249	o sar	oiens	5										
	<2	220> 221> 222>	CDS	(2	249)											
-	cgc	-	tgc	-			-	-	_		_		_	ccg Pro 15		48
				_										aac Asn		96
														gat Asp		144
						-						_		aag Lys	-	192 ;
			-	_	-	-	_		-	_		_		gag G1u	_	240
ccg	aga	tga														249

511

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Pro Arg *
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<210> 372 <211> 82 <212> PRT <213> Homo sapiens

<400> 372

 Met Arg Asp Asp Cys Asp Ile Asn Asp Asp Glu Phe Leu His Leu Pro Ala

 1
 5

 His Leu Arg Val Val Gly Pro Gln Gln Leu His Ser Glu Thr Asn Glu 20

 Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35

 Val Asp Gln Ala Leu Trp Glu Glu Glu Val Leu Gln Lys Glu Lys Lys 50

 Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65

 Pro Arg

<210> 373 <211> 219 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(219) <221> misc\_feature <222> (1)...(219) <223> n = A.T.C or G

<400> 373

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Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Ala Xaa Leu

1 5 10 15

96

nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc tca gcc cat Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His 20 25 30

tac gca aac ctg gcg ggt cca acc aac ccc gct ctg ccg ccg ctg ctg 144 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga 192 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly 50 55 aat acc acg cac tgc ccc ttc gcc tag 219 Asn Thr Thr His Cys Pro Phe Ala \* 65 · 70 <210> 374 <211> 72 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(72) <223> Xaa = Any Amino Acid <400> 374 Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Ala Xaa Leu 1 5 10 Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Ser Ala His 25 30 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu 40 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly Asn Thr Thr His Cys Pro Phe Ala 65 70 <210> 375 <211> 579 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(579)

	gcc	ссс	-			-	-			_	_	tcc Ser		_	. 48
												gcc Ala ·30			96
-	_		_	_	-						-	gct Ala	_		144
	-	_	_			_	_			-	-	ctt Leu	-		192
												ttc Phe			240
												ctg Leu			288
			_	-								gag Glu 110		-	336
		-		_	-	-	_	_	 -	-		acc Thr			. 384
	-	-	_									999 Gly			432
_	_			_							_	gac Asp			480
_			-	-							-	gct Ala			528

514

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
180
185
579

<210> 376 <211> 192 <212> PRT

<213> Homo sapiens

<400> 376

Met Ala Pro Lys Pro Gly Ala Glu Trp Ser Thr Ala Leu Ser His Leu 10 Val Leu Gly Val Val Ser Leu His Ala Ala Val Ser Thr Ala Glu Ala Ser Arg Gly Ala Ala Ala Gly Phe Leu Leu Gln Val Leu Ala Ala Thr Thr Thr Leu Ala Pro Gly Leu Ser Thr His Glu Asp Cys Leu Ala Gly 55 Ala Trp Val Ala Thr Val Ile Gly Leu Pro Leu Leu Ala Phe Asp Phe His Trp Val Asn Gly Asp Arg Ser Ser Ala Asn Leu Leu Gly Gly 90 Gly Met Val Leu Ala Val Ala Gly Gly His Leu Gly Pro Glu Gly Arg 105 Ser Val Ala Gly Gln Ala Met Leu Leu Val Val Ala Val Thr Ile Leu 120 Ile Val Ala Val Phe Thr Ala Asn Thr Tyr Gly Met Trp Gly Gly Ala 130 135 Met Leu Gly Val Ala Gly Leu Leu Ser Arg Leu Glu Glu Asp Arg Leu 150 155 Leu Leu Leu Pro Lys Glu Asp Val Cys Arg Trp Ala Leu Ala Val Gly 165 170 Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu 180 185 190

<210> 377 <211> 606

515

<212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(606) <400> 377 atg acc gtg cag aga ctc gtg gcc gcg gcc gtg ctg gtg gcc ctg gtc 48 Met Thr Val Gln Arg Leu Val Ala Ala Ala Val Leu Val Ala Leu Val 5 1 10 15 tca ctc atc ctc aac aac gtg gcg gcc ttc acc tcc aac tgg gtg tgc 96 Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 25 cag acg ctg gag gat ggg cgc agg cgc agc gtg ggg ctg tgg agg tcc 144 Gin Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 tgc tgg ctg gtg gac agg acc cgg gga ggg ccg agc cct ggg gcc aga 192 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 gcc ggc cag gtg gac gca cat gac tgt gag gcg ctg ggc tgg ggc tcc 240 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 80 gag gca gcc ggc ttc cag gag tcc cga ggc acc gtc aaa ctg cag ttc 288 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe 85 90 336 gac atg atg cgc gcc tgc aac ctg gtg gcc acg gcc gcg ctc acc gca Asp Met Met Arg Ala Cys Asn Leu Val Ala Thr Ala Ala Leu Thr Ala 100 105 110 384 Gly Gln Leu Thr Phe Leu Leu Gly Leu Val Gly Leu Pro Leu Leu Ser 115 120 125 ccc gac gcc ccg tgc tgg gag gag gcc atg gcc gct gca ttc caa ctg 432 Pro Asp Ala Pro Cys Trp Glu Glu Ala Met Ala Ala Ala Phe Gln Leu 130 135 140

	g agt a Ser 5																480
	a tac o Tyr			-										-	-		528
	t ctg u Leu	_	-	_		_	-	_									576
	a ggg g Gly																606
	<	210> 211> 212> 213>	201 PRT	o sap	oiens	5											
Me <sup>-</sup>	< t Thr	400> Val		Arg 5	Leu	Val	Ala	Ala	Ala 10	Val	Leu	Val	Ala	Leu 15	Val		
	^ Leu	Пe	Leu 20	_	Asn	Val	Ala <sub>.</sub>	A1 a 25		Thr	Ser	Asn	Trp 30		Cys		
Gli	n Thr	Leu 35		Asp	Gly	Arg	Arg 40		Ser	Val	Gly	Leu 45		Arg	Ser	•	
Cys	50 50	Leu	Val	Asp	Arg	Thr 55	Arg	Gly	Gly	Pro	Ser 60	Pro	Gly	Ala	Arg		
A1a 65	a Gly	Gln	Val	Asp	A1a 70	His	Asp	Cys	Glu	A1a 75	Leu	Gly	Trp	Gly	Ser 80		
G٦ι	ı Ala	Ala	Gly	Phe 85	Gln	Glu	Ser	Arg	Gly 90	Thr	Val	Lys	Leu	G1n 95	Phe		
Asp	) Met	Met	Arg 100	Ala	Cys	Asn	Leu	Val 105	Ala	Thr	Ala	Ala	Leu 110		Ala		
Gly	/ Gln	Leu 115		Phe	Leu	Leu	Gly 120		Val	Gly	Leu	Pro 125		Leu	Ser		
Pro	Asp 130		Pró	Cys	Trp	Glu 135		Ala	Met	Ala	Ala 140		Phe	Gln	Leu		
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	Tyr	Thr	Asn	Leu		Trp	Ser	Cys	Tyr		Asn	Ile	Gly	Ala			

				165					170					175		
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518

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Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
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Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
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10

15

1

						gca Ala					_	_		_	-	96
						aaa Lys					_					144
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						agc Ser							-	_		240
	gga Gly					aag Lys	tga *									264
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Lys	Pro	Asp 35		Ser	Gly	Lys	Asp 40		Lys	Pro	Asp	Phe 45		Lys	Phe	
Leu	Ser 50	-	Leu	Gly	Thr	G1ս 55		Ile	Glu	Asn	Ala 60		Glu	Phe	Пe	
Leu 65	Arg	Ser	Met	Ser	Arg 70	Ser	Thr	Gly	Phe	Met 75		Phe	Asp	Asp	Asn 80	
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520

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65

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522

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			-	-										tca Ser 95		2	288
-	_	-	_										_	gac Asp	-	3	336
	ctt Leu		tgg Trp	tga *												3	351
		210> 211> 212> 213>	116	sar	oiens	5											
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Glu	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40	Ala	Met	Leu	Tyr	Leu 45	Lys	Gly	Ala		
Gln	Gly 50	Arg	Arg	Phe	Ile	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser		
Asp 65		Pro	Leu	Pro	G1u 70		Arg	Ser	Pro	Asn 75		Gln	Leu	Leu	Thr 80		
	Pro	Glu	Ala	A1a 85		Ile	Leu	Leu	A1a 90		Leu	Gln	Lys	Ser 95			
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Asp	Phe	Lys 35	Tyr	Ala	Leu	Пe	Gly 40	Thr	Ala	Val	Gly	Val 45	Ala	Ile	Ser	
Ala	Glу 50	Phe	Leu	Ala	Leu	Lys 55	Ile	Cys	Met	Пе	Arg 60	Arg	His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70	Leu	Lys	Ser	Thr	Pro 75	Gly	Gly	Leu	Ser	Asp 80	
Thr	Ile	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95	Ser	
Lys	Arg	Asp	Ala 100	Gln	Val	Ile	Glu	Leu 105					,			
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527 Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 65 70 . 75 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 294 ttc tga Phe \* <210> 394 <211> 97 <212> PRT <213> Homo sapiens <400> 394 Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu 10 Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg 25 Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 55 60 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu

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Phe

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<211> 303

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529

Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser 50 55 Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile 70 75 Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met 90 . 85 Glu Asn Glu Thr 100 <210> 397 <211> 141 · <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(141) <400> 397 48 Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn 1 5 10 15 ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg 96 Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu 25 20 gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga 141 Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu \* 35 40 45 <210> 398 <211> 46 <212> PRT <213> Homo sapiens <400> 398 Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn 5 10 Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu 25 Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu 35 40 45

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				_								_	gag Glu	-	144
													agt Ser		192
	-			_		-	_						gaa Glu		240
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	gta Val						tga *								360

531

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	_	-	-		•	aaa Lys 55	•	•					-			1	.92
-						cat His	_			-	-			-		2	240
		-	-			aat Asn				-			_			2	88
						gct Ala					_	_	-			3	36
						aat Asn										3	84
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			-	-		tac Tyr				-			tag *			4	74
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1				5		Asn			10					15			
Ser	Leu	Leu	Leu 20	Leu	Leu	Val	Val	Cys 25	Gly	Ile	Gly	Cys	Val 30	Trp	His		
Trp		His 35	Arg	Val	Ala	Thr	Arg 40	Phe	Thr	Leu	Pro	Arg 45		Leu	Gln		
Arg			Ser	Arg	Arg	Lys 55		Cys	Thr	Lys	Thr 60		Leu	Gly	Pro		

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Lys	Ser	Ala	Val	Arg 85	Gly	Asn	Asn	Thr	His 90	Asp	Asn	Tyr	Glu	Asn 95		
Glu	Ala	Gly	Pro 100	Pro	Lys	Ala	Lys	Gly 105	Lys	Thr	Asp	Lys	G1u 110	Leu	Tyr	
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Pro 145	Gln	Asp	Glu	Asp	Ile 150	Tyr	Ile	Leu	Pro	Asp 155	Ser	Tyr				
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			-	-			-		_				cac His 30	-	_	96
													gaa Glu			144
			-		-	_	-	-	-	-			cta Leu		•	192
	cac	aca	caa	ata	ata	agc	ctt	aag	gac	aag	cta	gaa	ttt	gcc	ccg	240
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534

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn \* 85 90

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<211> 92

<212> PRT

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<400> 404

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Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30

Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 45

Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 80

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn 85 90

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1 5 10 15

cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20 25 30

96

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt . 144 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser

35 40 45

535

gga atg aat toa gtt agc too att cag aac caa atg cag too aag gga 192 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 50 ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat 240 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 75 acg aag gcg gga tag 255 Thr Lys Ala Gly \* <210> 406 <211> 84 <212> PRT <213> Homo sapiens <400> 406 Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20 25 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 40 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 75 65 70 80 Thr Lys Ala Gly <210> 407 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 407 48

536

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		-	-		gga Gly								_	_		192
					gct Ala 70					-	-	_	-		-	240
	agc Ser	tga *														249
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Arg	Ile	Leu 35	Asn	Thr	Gly	Leu	Asp 40		Glu	Thr	Leu	Ser 45		Cys	Val	
Arg	Leu 50		Glu	Gln	Gly	Ile 55		Pro	Glu	Ala	Leu 60		Ser	Val	Пе	
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Thr Ser

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ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                       96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
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						gat Asp										240
					Xaa	gac Asp	Ser	Asp	Asp	Phe						288
						ctg Leu						-	-			336
gtt Val	gtc Val	cat His 115	cga Arg	atc Ile	ctc Leu	aaa Lys	999 Gly 120	aaa Lys	atc Ile	act Thr	ggt Gly	gct Ala 125	ttg Leu	aac Asn	tcg Ser	384
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Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
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Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
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		tca Ser							_	_				•	240
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		aag Lys 100			_	_		-						-	336
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caa gaa atc aat aaa ggt ggg ata gat gca gta gaa agt ctt atg ata Gln Glu Ile Asn Lys Gly Gly Ile Asp Ala Val Glu Ser Leu Met Ile 65 70 75 80	240
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tgt tca cag aat ggc ttt gac aaa tta tct aat gac atc acg tct att Cys Ser Gln Asn Gly Phe Asp Lys Leu Ser Asn Asp Ile Thr Ser Ile 100 105 110	336
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Leu His Leu Phe Ser Ala Asp Met Lys Lys Val Gly Ile Lys Leu Leu 50 55 60	
Gln Glu Ile Asn Lys Gly Gly Ile Asp Ala Val Glu Ser Leu Met Ile	

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546

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50

55

60

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Trp Lys Leu Gln Asp Gly Cys Arg Gly Pro Trp Thr Leu Leu Ala 65 70 75

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